

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/44, 31/495	A1	(11) International Publication Number: WO 97/36587
		(43) International Publication Date: 9 October 1997 (09.10.97)

(21) International Application Number: PCT/US97/05328

(22) International Filing Date: 31 March 1997 (31.03.97)

(30) Priority Data:

60/014,773

3 April 1996 (03.04.96)

US

9613599.1

28 June 1996 (28.06.96)

GB

(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HEIMBROOK, David, C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). OLIFF, Allen, I. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). STIRDIVANT, Steven, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published*With international search report.*

(54) Title: A METHOD OF TREATING CANCER

(57) Abstract

The present invention relates to a method of treating cancer which comprises administering to a mammalian patient a compound which inhibits Raf and a compound which inhibits farnesyl protein transferase.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

-1-

TITLE OF THE INVENTION
A METHOD OF TREATING CANCER

BACKGROUND OF THE INVENTION

5 The present invention relates to a method of treating cancer using a combination of a compound which has Raf antagonist activity and a compound which has farnesyl transferase inhibiting activity.

 The Raf antagonist compounds used in the present invention demonstrate anti-cancer activity through antagonism of the kinase, Raf .
10 The *raf* genes code for a family of proteins which can be oncogenically activated through N-terminal fusion, truncation or point mutations. Raf is a member of the MAP Kinase cascade, which also includes MEK's and MAP Kinase (ERK). Raf can be activated and undergoes rapid phosphorylation in response to treatment of cells with PDGF, EGF,
15 insulin, thrombin, endothelin, acidic FGF, CSF1 or TPA, as well as in response to oncoproteins v-fms, v-src, v-sis, Hras and polyoma middle T antigen. Antisense constructs which reduce cellular levels of c-Raf, and hence Raf activity, inhibit the growth of oncogene-transformed rodent fibroblasts in soft agar, while exhibiting little or no general
20 cytotoxicity. Since inhibition of growth in soft agar is highly predictive of tumor responsiveness in whole animals, these studies suggest that the antagonism of Raf is an effective means by which to treat cancers in which Raf plays a role.

 Examples of cancers where Raf is implicated through
25 overexpression include cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung. More particularly, such examples include histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers. Additional examples include cancers in which overexpression or activation of Raf-activating oncogenes (e.g., K-*ras*,
30 *erb-B*) is observed. More particularly, such cancers include pancreatic and breast carcinoma.

 The Ras protein is part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action

-2-

indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation, Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Activation of Ras leads to activation of multiple intracellular signal transduction pathways, including the MAP Kinase pathway and the Rho/Rac pathway (Joneson *et al.*, *Science* 271:810-812).

Mutated *ras* genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

The Ras protein is one of several proteins that are known to undergo post-translational modification. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, 62:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer *et al.*, *Science*, 249:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)).

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the

-3-

CAAX motif with a C₁₅ or C₂₀ isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first class includes analogs of farnesyl diphosphate (FPP), while the second is related to protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, 37, 725 (1994)).

Inhibition of farnesyl-protein transferase has been shown to block the growth of *ras*-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993) and G.L. James *et al.*, *Science*, 260:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci*

-4-

U.S.A., 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995)).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells.

A Raf antagonist compound and a farnesyl protein transferase inhibitor are used in the present invention to treat cancer, such as in tumor cells which are not particularly Raf or FPTase dependent. The Raf antagonist compound and a farnesyl protein transferase inhibiting compound are used in combination.

SUMMARY OF THE INVENTION

A method of treating cancer is disclosed which is comprised of administering to a mammalian patient in need of such treatment an effective amount of a Raf antagonist compound and an effective amount of a farnesyl protein transferase inhibiting compound.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of treating cancer which is comprised of administering to a mammalian patient in need of such treatment an effective amount of a Raf antagonist compound and an effective amount of a farnesyl protein transferase inhibiting compound. Any compound which antagonizes Raf and any compound which inhibits farnesyl protein transferase can be used.

As used herein the term Raf antagonist is used in the general sense to relate to compounds which antagonize, inhibit or counteract the activity of the *raf* gene or the protein produced in response thereto.

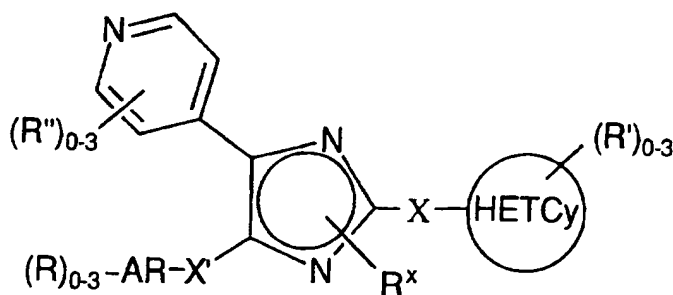
-5-

The term farnesyl protein transferase inhibiting compound is likewise used in the general sense and refers to compounds which antagonize, inhibit or counteract the activity of the gene coding farnesyl protein transferase or the protein produced in response thereto.

- 5 Cancers which are treatable in accordance with the invention described herein include cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx, liver and lung. More particularly, such cancers include histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers. Additional examples include cancers in which
 10 overexpression or activation of Raf-activating oncogenes (e.g., *K-ras*, *erb-B*) is observed. More particularly, such cancers include pancreatic, mammary and salivary carcinomas, colorectal carcinoma, exocrine pancreatic carcinoma and myeloid leukemias.

15 Examples of compounds which antagonize Raf are as follows:

- (a) a compound represented by formula (I-a):



(I-a)

20

or a pharmaceutically acceptable salt thereof, wherein:

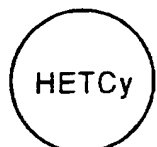
AR represents an aromatic group containing 6-10 atoms;

25

X and X' each independently represent $-(CH_2)_m-Y-(CH_2)_n-$, wherein m and n represent integers within the range of from 0 - 4, such that the sum of m and n is from 0 - 6; Y represents a member selected from the group consisting of: a direct bond; O ; $S(O)_y$, with y equal to

-6-

0, 1 or 2; $\text{NR}^{\text{q}'}$, with $\text{R}^{\text{q}'}$ as defined below; $\text{C}(\text{O})$; $\text{OC}(\text{O})$; $\text{C}(\text{O})\text{O}$;
 $\text{SO}_x\text{NR}^{\text{q}'}$ with x equal to 1 or 2 and $\text{R}^{\text{q}'}$ as defined below; $\text{NR}^{\text{q}'}\text{SO}_x$;
 $\text{C}(\text{O})\text{NR}^{\text{q}'}$ and $\text{NR}^{\text{q}'}\text{C}(\text{O})$;



represents a 4 to 10 membered non-aromatic heterocycle containing at least one N atom, and optionally containing 1-2 additional N atoms and 0-1 O or S atom;

- 5 R^x represents H, C_{1-6} alkyl(R^{q})₃, OC_{1-6} alkyl(R^{q})₃ or $\text{C}(\text{O})\text{C}_{1-6}$ alkyl(R^{q})₃;

- each R and R'' independently represents a member selected from the group consisting of: halo; hydroxy; C_{1-6} alkyl(R^{q})₃;
 10 OC_{1-6} alkyl(R^{q})₃; C_{3-8} cycloalkyl(R^{q})₃; CN; CONH_2 ; CONHC_{1-6} alkyl(R^{q})₃; $\text{CON}(\text{C}_{1-6}$ alkyl(R^{q})₃)₂; NH_2 ; NHC_{1-6} alkyl(R^{q})₃;
 $\text{N}(\text{C}_{1-6}$ alkyl(R^{q})₃)₂; CO_2H ; $\text{CO}_2\text{C}_{1-6}$ alkyl(R^{q})₃; $\text{C}(\text{O})\text{C}_{1-6}$ alkyl(R^{q})₃; aryl(R^{q})₃; heteroaryl(R^{q})₃; CF_3 ; SH; NO_2 ; $\text{SO}_y\text{C}_{1-6}$ alkyl(R^{q})₃, with y as defined above; SO_2NH_2 ; $\text{SO}_2\text{NHC}_{1-6}$ alkyl(R^{q})₃;
 15 $\text{SO}_2\text{N}(\text{C}_{1-6}$ alkyl(R^{q})₃)₂; $\text{NHSO}_2\text{C}_{1-6}$ alkyl(R^{q})₃, $\text{NHSO}_2\text{aryl}(\text{R}^{\text{q}})$ ₃, $\text{NHSO}_2\text{heteroaryl}(\text{R}^{\text{q}})$ ₃, $\text{N}(\text{R}^{\text{q}})\text{C}(\text{O})\text{C}_{1-6}$ alkyl(R^{q})₃; $\text{NR}^{\text{q}'}\text{C}(\text{O})\text{NH}(\text{C}_{1-6}$ alkyl(R^{q})₃);
 C_{2-4} alkenyl(R^{q})₂₋₃ and C_{2-4} alkynyl(R^{q})₁₋₃;

- 20 each R' independently represents a member selected from the group consisting of: CONH_2 ; CONHC_{1-6} alkyl(R^{q})₃;
 $\text{CON}(\text{C}_{1-6}$ alkyl(R^{q})₃)₂; CONHC_{3-8} cycloalkyl(R^{q})₃;
 $\text{CON}(\text{C}_{3-8}$ cycloalkyl(R^{q})₃)₂; CO_2H ; $\text{CO}_2\text{C}_{1-6}$ alkyl(R^{q})₃;
 $\text{C}(\text{O})\text{C}_{1-6}$ alkyl(R^{q})₃; $\text{CO}_2\text{C}_{3-8}$ cycloalkyl(R^{q})₃;
 25 $\text{C}(\text{O})\text{C}_{3-8}$ cycloalkyl(R^{q})₃; $-\text{[C}(\text{O})(\text{CH}_2)_j\text{-CR}^5\text{R}^6\text{-(CH}_2)_k\text{-NR}^7\text{]}_p\text{-R}^8$;
 $-\text{C}(\text{O})\text{C}_{3-8}$ cycloalkyl(R^{q})₃; $-\text{C}(\text{O})\text{heterocycl}(\text{R}^{\text{q}})$ ₃; $\text{CON}[\text{C}_{1-6}$ alkyl(R^{q})₃][C_{3-8} cycloalkyl(R^{q})₃]; $\text{C}(\text{O})\text{aryl}(\text{R}^{\text{q}})$ ₃ ,
 $\text{C}(\text{O})\text{heteroaryl}(\text{R}^{\text{q}})$ ₃ ;

-7-

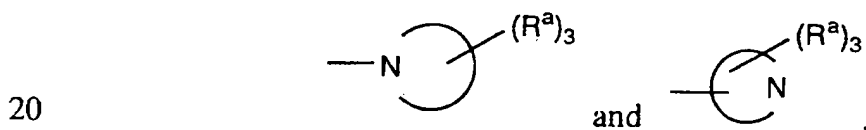
wherein p represents 1, 2 or 3;

j and k are integers independently selected from 0 - 3;

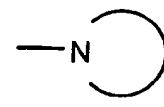
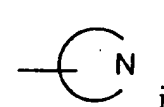
each R^5 and R^6 independently represents H, aryl, C_{1-6} alkyl(R^q)₃, or each CR^5R^6 taken in combination represents a 3, 4, 5 or 6 membered cycloalkyl or heterocyclyl group, an aryl group or a heteroaryl group, wherein when p equals 1, at least one of j and k is 1, 2 or 3;

each R^7 and R^8 independently represents H, C_{1-6} alkyl or aryl;

R^q represents a member selected from the group consisting of: R^q ; CN; CO_2H ; CO_2C_{1-4} alkyl; $C(O)C_{1-4}$ alkyl; aryl(R^a)₃; NH_2 ; NHC_{1-6} alkyl(R^a)₃; $N(C_{1-6}$ alkyl(R^a)₃)₂; heteroaryl(R^a)₃; $CONH_2$; SH ; $S(O)_y$ C_{1-6} alkyl(R^a)₃; $C(O)NHC_{1-6}$ alkyl(R^a)₃; $C(O)N(C_{1-6}$ alkyl(R^a)₃)₂; -heteroalkyl(R^a)₃; - $NHC(O)NH_2$; - $NHC(NH)NH_2$;



wherein

 and  independently represent mono or bicyclic ring systems, non-aromatic or partially aromatic, containing from 5-10 ring atoms, 1-4 of which are N and 0-1 of which are O or $S(O)_y$, with y equal to 0, 1 or 2, optionally containing 1-2 carbonyl groups;

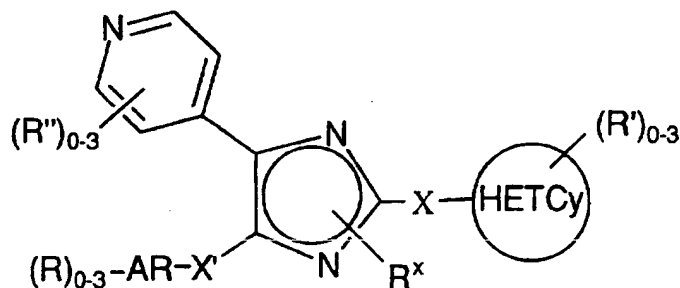
each R^a independently represents a member selected from the group consisting of: H, C_{1-6} alkyl, OC_{1-6} alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aralkoxy, substituted

-8-

- aralkoxy, halo, hydroxy, CN, CONH₂, CONHC₁₋₆ alkyl, CON(C₁₋₆ alkyl)₂, CO₂H, CO₂C₁₋₆ alkyl, C(O)C₁₋₆ alkyl, phenyl, CF₃, SH, NO₂, SO_yC₁₋₆ alkyl, with y as defined above; SO₂NH₂, SO₂NHC₁₋₆ alkyl, NHSO₂(substituted aryl), NHSO₂(substituted heteroaryl),
- 5 NHSO₂C₁₋₆alkyl, NHSO₂aryl, NHSO₂heteroaryl, NH₂, NHC₁₋₆ alkyl, N(C₁₋₆ alkyl)₂, NHC(O)C₁₋₆ alkyl, NHC(O)NH(C₁₋₆ alkyl), C₂₋₄ alkenyl and C₂₋₄ alkynyl;

- and R^{q'} represents H, OH, C₁₋₄ alkyl, -OC₁₋₄ alkyl, aryl
- 10 or C(O)C₁₋₄ alkyl;

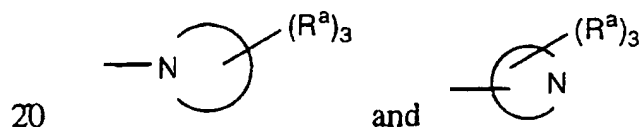
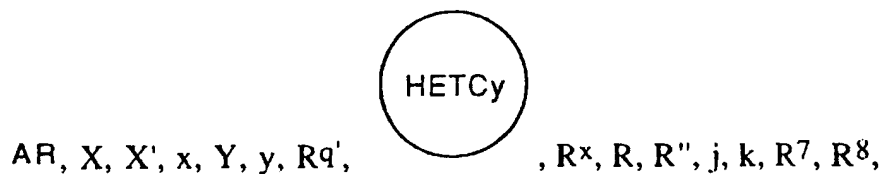
(b) a compound represented by formula (I-b)



(I-b)

15

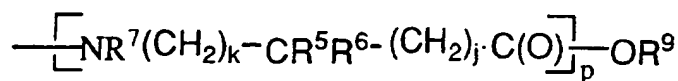
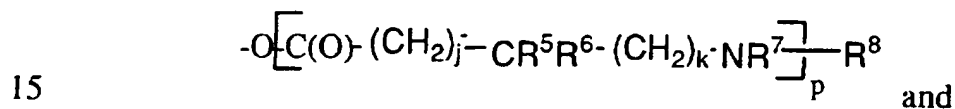
or a pharmaceutically acceptable salt thereof, wherein:



are as defined above with respect to formula (I-a);

-9-

- each R' independently represents a member selected from the group consisting of: hydroxy; C₁₋₆ alkyl(R^q)₃; C₃₋₈ cycloalkyl(R^q)₃; OC₁₋₆ alkyl(R^q)₃; OC₃₋₈ cycloalkyl(R^q)₃; heterocyclyl(R^q)₃; CN; NH(R^q"); NHC₁₋₆ alkyl(R^q)₃; N(C₁₋₆ alkyl(R^q)₃)₂; NHC₃₋₈ cycloalkyl(R^q)₃; N(C₃₋₈ cycloalkyl(R^q)₃)₂; CF₃; SH; NO₂; C₂₋₄ alkenyl(R^q)₂₋₃, aryl(R^q)₃, heteroaryl(R^q)₃; C₂₋₄ alkynyl(R^q)₁₋₃; -OC(O)C₃₋₈ cycloalkyl(R^q)₃; SO₂NH₂; SO₂NHC₁₋₆ alkyl(R^q)₃; SO₂N(C₁₋₆ alkyl(R^q)₃)₂; NHSO₂C₁₋₆ alkyl(R^q)₃, NHSO₂aryl(R^q)₃, NHSO₂heteroaryl(R^q)₃,
 10 -OC(O)heterocyclyl(R^q)₃; N(R^q)C(O)C₁₋₆ alkyl(R^q)₃; NR^qC(O)NH(C₁₋₆ alkyl(R^q)₃); -OC(O)C₁₋₆ alkyl(R^q)₃; -OC(O)aryl(R^q)₃, -OC(O)heteroaryl(R^q)₃; -C(=NR^q)NH₂; -C(=N^q)NHC₁₋₆ alkyl(R^q)₃, -C(=N^q)N(C₁₋₆ alkyl(R^q)₃)₂;



- 20 R⁵ and R⁶ are independently H, aryl, C₁₋₆ alkyl(R^q)₃, or CR⁵R⁶ in combination represents a 3, 4, 5 or 6 membered cycloalkyl or heterocyclyl group, an aryl group or a heteroaryl group;

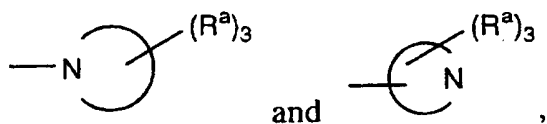
- 25 p represents 1, 2 or 3, with the proviso that when p represents 1, CR⁵R⁶ represents a 3, 4, 5 or 6 membered cycloalkyl group or a heterocyclyl group, an aryl group or a heteroaryl group, and at least one of j and k is 1, 2 or 3;

- 30 R⁹ represents H, a negative charge balanced by a positively charged group or a protecting group;

R^q represents a member selected from the group consisting of: R^q; CN; CO₂H; CO₂C₁₋₄ alkyl; C(O)C₁₋₄ alkyl; NH(R^q"); aryl(R^a)₃; heteroaryl(R^a)₃; NHC₁₋₄ alkyl; N(C₁₋₄ alkyl)₂; CONH₂;

-10-

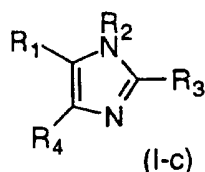
SH; S(O)_y C₁₋₆ alkyl(R^a)₃; C(O)NHC₁₋₆ alkyl(R^a)₃; C(O)N(C₁₋₆ alkyl(R^a)₃)₂; NHC(NH)NH₂; -heteroalkyl(R^a)₃; -NHC(O)NH₂;



5

and R^{q''} represents H, OH or OC₁₋₄ alkyl,

and (c) a compound represented by formula (I-c):



10

or a pharmaceutically acceptable salt thereof,
wherein:

15 R₁ is 4-pyridyl, pyrimidinyl, quinazolin-4-yl, quinolyl, isoquinolinyl, 1-imidazolyl or 1-benzimidazolyl which is optionally substituted with one or two substituents each of which is independently selected from C₁₋₄ alkyl, halogen, C₁₋₄ alkoxy, C₁₋₄ alkylthio, NR₁₀R₂₀, or N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or

20 NR₂₂;

R₂ is hydrogen, -(CR₁₀R₂₀)_n OR₁₂, heterocyclyl, heterocyclyl C₁-10 alkyl, C₁-10 alkyl, halo-substituted C₁-10 alkyl, C₂-10 alkenyl, C₂-10 alkynyl, C₃-7 cycloalkyl, C₃-7 cycloalkyl C₁-10 alkyl, C₅-7 cycloalkenyl, aryl, aryl C₁-10 alkyl, heteroaryl, heteroaryl C₁-10 alkyl, (CR₁₀R₂₀)_nOR₁₃, (CR₁₀R₂₀)_nS(O)_mR₂₅, (CR₁₀R₂₀)_nNHS(O)₂R₂₅, (CR₁₀R₂₀)_nNR₈R₉, (CR₁₀R₂₀)_nNO₂, (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nS(O)_mNR₈R₉, (CR₁₀R₂₀)_nC(Z)R₁₃, (CR₁₀R₂₀)_nC(Z)OR₁₃, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₈R₉, (CR₁₀R₂₀)_nC(Z)NR₁₃OR₁₂, (CR₁₀R₂₀)_nNR₁₀C(Z)R₁₃, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₈R₉,

-11-

- (CR₁₀R₂₀)_n'N(OR₂₁)C(Z)NR₈R₉, (CR₁₀R₂₀)_n'N(OR₂₁)C(Z)R₁₃,
 (CR₁₀R₂₀)_n'C(=NOR₂₁)R₁₃, (CR₁₀R₂₀)_n'NR₁₀C(=NR₂₇)NR₈R₉,
 (CR₁₀R₂₀)_n'OC(Z)NR₈R₉, (CR₁₀R₂₀)_n'NR₁₀C(Z)NR₈R₉,
 (CR₁₀R₂₀)_n'C(Z)OR₁₀, 5-(R₂₅)-1,2,4-oxadiazol-3-yl or 4-(R₁₂)-
 5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl,
 arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or
 heterocyclyalkyl moieties may be optionally substituted;
 n' is an integer having a value of 1 to 10;
 m is 0 or the integer 1 or 2;
 R₃ is Q-(Y₁)_t;
 Q is an aryl or heteroaryl group;
 t is a number having a value of 1, 2 or 3;
 Z is oxygen or sulfur;
 n is 0 or an integer from 1 to 10;
 Y₁ is independently selected from hydrogen, C₁₋₅ alkyl, halo-
 substituted C₁₋₅ alkyl, halogen, or -(CR₁₀R₂₀)_nY₂;
 Y₂ is -OR₈, -NO₂, -S(O)_m'R₁₁, -SR₈, -S(O)_m'OR₈, -S(O)_mNR₈R₉,
 -NR₈R₉, -O(CR₁₀R₂₀)_nNR₈R₉, -C(O)R₈, -CO₂R₈,
 -CO₂(CR₁₀R₂₀)_nCONR₈R₉, -ZC(O)R₈, -CN, -C(Z)NR₈R₉,
 NR-NR₁₀C(Z)R₈, -C(Z)NR₈OR₉, -NR₁₀C(Z)NR₈R₉,
 -NR₁₀S(O)_mR₁₁, -N(OR₂₁)C(Z)NR₈R₉, -N(OR₂₁)C(Z)R₈,
 -C(=NOR₂₁)R₈, -NR₁₀C(=NR₁₅)SR₁₁, -NR₁₀C(=NR₁₅)NR₈R₉,
 -NR₁₀C(=CR₁₄R₂₄)SR₁₁, -NR₁₀C(=CR₁₄R₂₄)NR₈R₉,
 -NR₁₀C(O)C(O)NR₈R₉, -NR₁₀C(O)C(O)OR₁₀,
 -C(=NR₁₃)NR₈R₉, -C(=NOR₁₃)NR₈R₉, -C(=NR₁₃)ZR₁₁,
 -OC(Z)NR₈R₉, -NR₁₀S(O)_mCF₃, -NR₁₀C(Z)OR₁₀, 5-(R₁₈)-
 1,2,4-oxadiazol-3-yl or 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-
 oxadiazol-3-yl;
 m' is a number having a value of 1 or 2;
 R₄ is phenyl, naphth-1-yl or naphth-2-yl which is optionally substituted
 by one or two substituents, each of which is independently selected,
 and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-1-yl
 substituent, is halo, cyano, -C(Z)NR₇R₁₇, -C(Z)OR₂₃,
 -(CR₁₀R₂₀)_m'COR₃₆, SR₅, -SOR₅, OR₃₆, halo-substituted-C₁₋₄

-12-

- alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃ or
 -(CR₁₀R₂₀)_m"NR₁₀R₂₀ and which, for other positions of
 substitution, is halo, cyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈,
 -(CR₁₀R₂₀)_m"COR₈, -S(O)_mR₈, -OR₈, halo-substituted-C₁₋₄
 5 alkyl, C₁₋₄ alkyl, -(CR₁₀R₂₀)_m"NR₁₀C(Z)R₈, -NR₁₀S(O)_mR₁₁,
 -NR₁₀S(O)_mNR₇R₁₇, -ZC(Z)R₈ or -(CR₁₀R₂₀)_mNR₁₆R₂₆;
 wherein m" is 0 to 5 and m'" is 0 or 1;
 R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇,
 excluding the moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being
 10 -SOH;
 R₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkenyl, C₂₋₄
 alkynyl or C₃₋₅ cycloalkyl;
 R₇ and R₁₇ are each independently selected from hydrogen or C₁₋₄
 alkyl, or R₇ and R₁₇ together with the nitrogen to which they are
 15 attached form a heterocyclic ring of 5 to 7 members which ring
 optionally contains an additional heteroatom selected from oxygen,
 sulfur or NR₂₂;
 R₈ is hydrogen, heterocyclyl, heterocyclylalkyl or R₁₁;
 R₉ is hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇
 20 cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylalkyl, heteroaryl or
 heteroarylalkyl or R₈ and R₉ may together with the nitrogen to
 which they are attached form a heterocyclic ring of 5 to 7 members
 which ring optionally contains an additional heteroatom selected
 from oxygen, sulfur or NR₁₂;
 25 R₁₀ and R₂₀ are each independently selected from hydrogen and C₁₋₄
 alkyl;
 R₁₁ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀
 alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylalkyl,
 heteroaryl or heteroarylalkyl;
 30 R₁₂ is hydrogen, -C(Z)R₁₃ or optionally substituted C₁₋₄ alkyl,
 optionally substituted arylC₁₋₄ alkyl or S(O)₂R₂₅;
 R₁₃ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl,
 heterocyclyl C₁₋₁₀ alkyl, aryl, aryl C₁₋₁₀ alkyl, heteroaryl or
 heteroaryl C₁₋₁₀ alkyl;

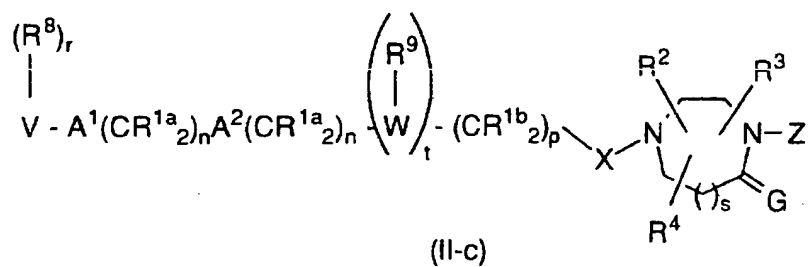
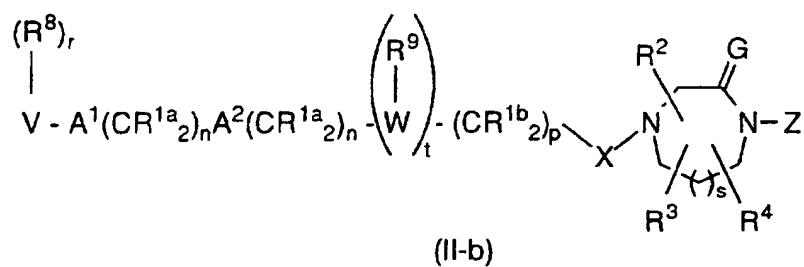
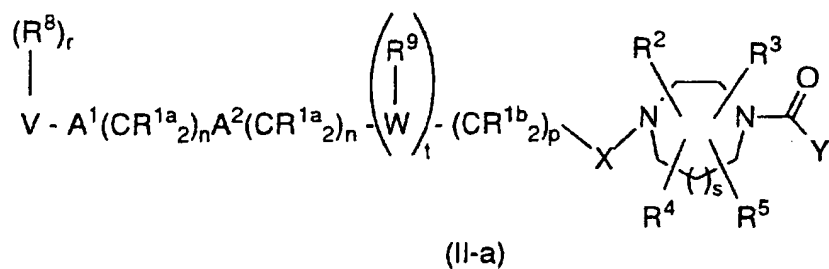
-13-

- R₁₄ and R₂₄ is each independently selected from hydrogen, alkyl, nitro or cyano;
- R₁₅ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;
- 5 R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;
- 10 R₁₈ and R₁₉ is each independently selected from hydrogen, C₁₋₄ alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together denote a oxygen or sulfur;
- R₂₁ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroarylalkyl, 15 heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;
- R₂₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;
- R₂₃ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl or C₃₋₅ cycloalkyl;
- R₃₆ is hydrogen or R₂₃;
- R₂₅ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, arylalkyl, 20 heterocyclyl, heterocyclyl-C₁₋₁₀ alkyl, heteroaryl or heteroarylalkyl;
- R₂₇ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl; or a pharmaceutically acceptable salt thereof.

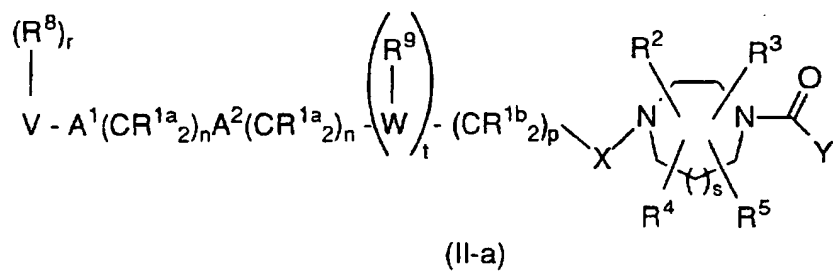
Examples of farnesyl protein transferase inhibiting 25 compounds include the following:

- (a) a compound represented by formula (II-a) through (II-c):

-14-



wherein with respect to formula (II-a):



5

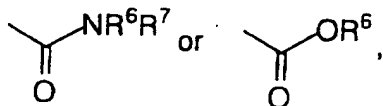
or a pharmaceutically acceptable salt thereof,

-15-

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl,
 C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 5 NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆
 alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 10 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;

R² and R³ are independently selected from: H; unsubstituted or
 substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl,
 15 unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,
 unsubstituted or substituted heterocycle,



wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁-4 alkyl,
 - b) (CH₂)_pOR⁶,
 - c) (CH₂)_pNR⁶R⁷,
 - d) halogen,
- 2) C₃-6 cycloalkyl,
- 3) OR⁶,
- 4) SR⁶, S(O)R⁶, SO₂R⁶,

-16-

- 5) $\text{—NR}^6\text{R}^7$,
- 6) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C(=O)—R}^7 \\ | \\ \text{O} \end{array}$,
- 7) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C(=O)—NR}^7\text{R}^{7a} \\ | \\ \text{O} \end{array}$,
- 8) $\begin{array}{c} \text{—O—C(=O)—NR}^6\text{R}^7 \\ | \\ \text{O} \end{array}$,
- 9) $\begin{array}{c} \text{—O—C(=O)—OR}^6 \\ | \\ \text{O} \end{array}$,
- 10) $\begin{array}{c} \text{—C(=O)—NR}^6\text{R}^7 \\ | \\ \text{O} \end{array}$,
- 11) $\text{—SO}_2\text{—NR}^6\text{R}^7$,
- 12) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—SO}_2\text{—R}^7 \end{array}$,
- 13) $\begin{array}{c} \text{—C(=O)—R}^6 \\ | \\ \text{O} \end{array}$, or
- 14) $\begin{array}{c} \text{—C(=O)—OR}^6 \\ | \\ \text{O} \end{array}$; or

5 R^2 and R^3 are attached to the same C atom and are combined to form $(\text{CH}_2)_u$ - wherein one of the carbon atoms is optionally replaced by a

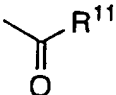
10 moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10}\text{)—}$;

-17-

R⁴ and R⁵ are independently selected from H and CH₃;

5 and any two of R², R³, R⁴ and R⁵ are optionally attached to the same carbon atom;

R⁶, R⁷ and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 10 a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,
 e) 
 f) —SO₂R¹¹, or
 15 g) N(R¹⁰)₂; or

R⁶ and R⁷ may be joined in a ring;
 R⁷ and R^{7a} may be joined in a ring;

20

R⁸ is independently selected from:

- a) hydrogen,
 b) aryl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 25 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
 c) C₁₋₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆
 30 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,

-18-

$R^{10}C(O)NH-$, CN , $H_2N-C(NH)-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{10}OC(O)NH-$;

R^9 is selected from:

- 5 a) hydrogen,
- b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , NO_2 , $(R^{10})_2N-C-(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
- 10 c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C-(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

- 15 R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

- 20 A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O , $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$, or $S(O)_m$;

V is selected from:

- 25 a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N,
- 30 and
- e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

-19-

W is a heterocycle;

X is $-\text{CH}_2-$, $-\text{C}(=\text{O})-$, or $-\text{S}(=\text{O})_m-$;

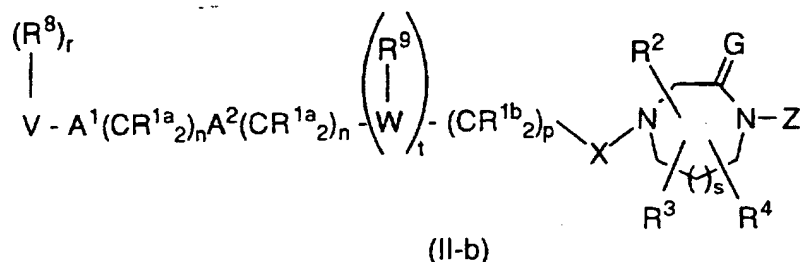
5 Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

- 1) C_{1-4} alkyl, unsubstituted or substituted with:
 - a) C_{1-4} alkoxy,
 - b) NR^6R^7 ,
 - 10 c) C_{3-6} cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO ,
 - f) $-\text{S}(\text{O})_m\text{R}^6$, or
 - 15 g) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR^6 ,
- 5) NR^6R^7 ,
- 6) CN ,
- 20 7) NO_2 ,
- 8) CF_3 ;
- 9) $-\text{S}(\text{O})_m\text{R}^6$,
- 10) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
- 25 11) $\text{C}_3\text{-C}_6$ cycloalkyl;

m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 30 s is 0 or 1;
 t is 0 or 1; and
 u is 4 or 5;

with respect to formula (II-b):

-20-



or a pharmaceutically acceptable salt thereof,

5 R^{1a}, R^{1b}, R¹⁰, R¹¹, m, R², R³, R⁶, R⁷, p, R^{7a}, u, R⁸, A¹, A², V, W, X, n, p, r, s, t and u are as defined above with respect to formula (II-a);

R⁴ is selected from H and CH₃;

10 and any two of R², R³ and R⁴ are optionally attached to the same carbon atom;

R⁹ is selected from:

- a) hydrogen,
- 15 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

G is H₂ or O;

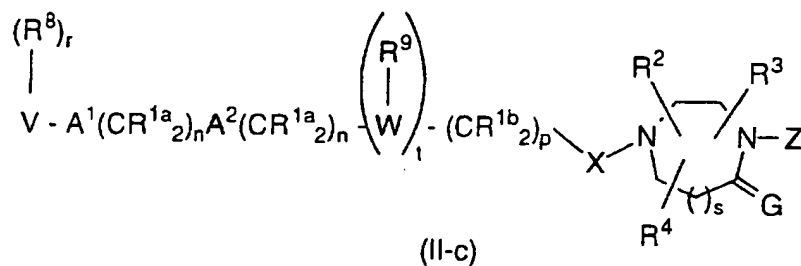
25- Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

- 1) C₁-4 alkyl, unsubstituted or substituted with:
 - a) C₁-4 alkoxy,

-21-

- 5 b) NR^6R^7 ,
 c) C₃₋₆ cycloalkyl,
 d) aryl or heterocycle,
 e) HO,
 f) $-\text{S}(\text{O})_m\text{R}^6$, or
 g) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
 2) aryl or heterocycle,
 3) halogen,
 4) OR^6 ,
 10 5) NR^6R^7 ,
 6) CN,
 7) NO_2 ,
 8) CF_3 ;
 9) $-\text{S}(\text{O})_m\text{R}^6$,
 15 10) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
 11) C_{3-C6} cycloalkyl;

with respect to formula (II-c):



20 or a pharmaceutically acceptable salt thereof,

R^{1a} , R^{1b} , R^{10} , R^{11} , m, R^2 , R^3 , R^6 , R^7 , p, u, R^{7a} , R^8 , A^1 , A^2 , V, W, X, n, r and t are as defined above with respect to formula (II-a);

25- R^4 is selected from H and CH_3 ;

and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

-22-

G is O;

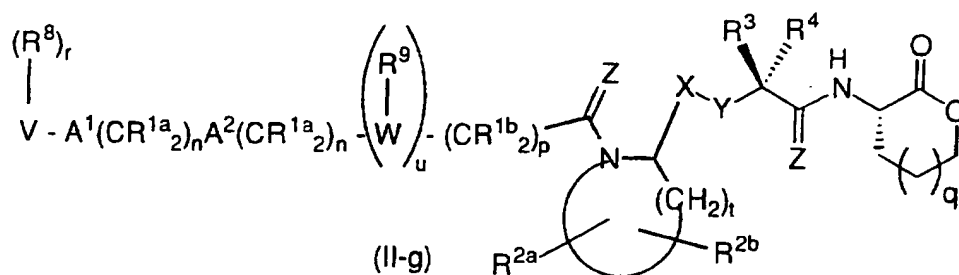
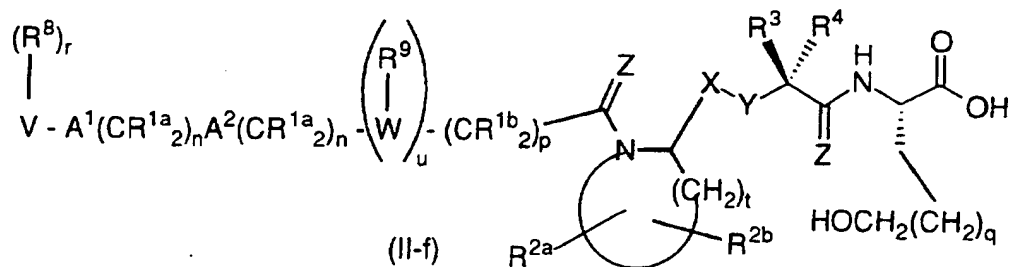
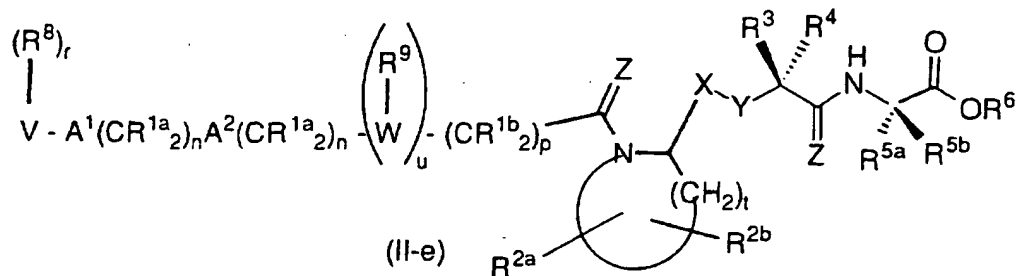
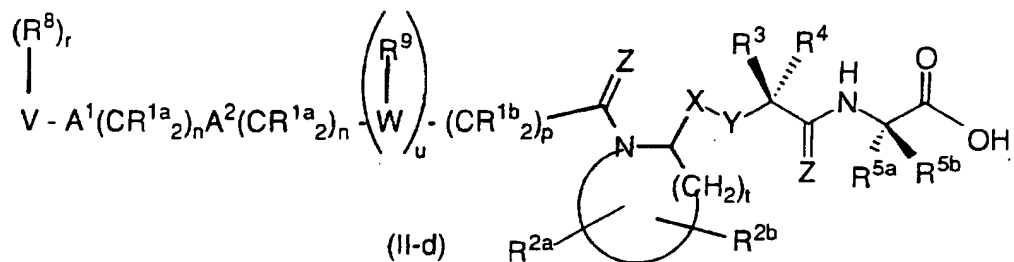
- 5 Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:
- 1) C₁₋₄ alkyl, unsubstituted or substituted with:
 - a) C₁₋₄ alkoxy,
 - b) NR⁶R⁷,
 - 10 c) C₃₋₆ cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - f) -S(O)_mR⁶, or
 - g) -C(O)NR⁶R⁷,
 - 15 2) aryl or heterocycle,
 - 3) halogen,
 - 4) OR⁶,
 - 5) NR⁶R⁷,
 - 6) CN,
 - 20 7) NO₂,
 - 8) CF₃;
 - 9) -S(O)_mR⁶,
 - 10) -C(O)NR⁶R⁷, or
 - 11) C₃₋₆ cycloalkyl;

25 and

s is I;

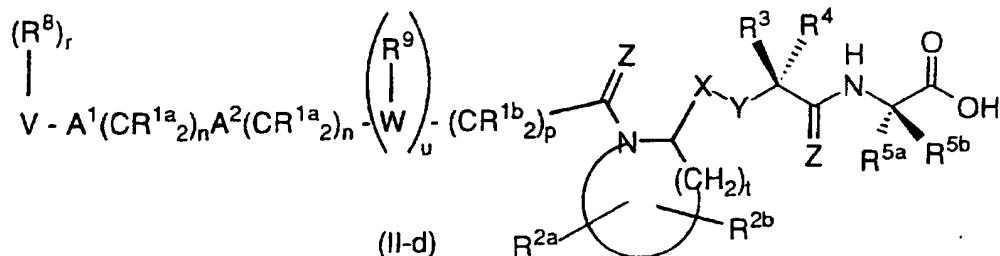
30 (b) a compound represented by formula (II-d) through (II-g):

-23-



wherein with respect to formula (II-d):

-24-



or a pharmaceutically acceptable salt thereof,

5 R^{11} , V , W , m , n , p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- 10 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- 15 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;

20

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N₃, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- 25 c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃,

-25-

- N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

5

R³ and R⁴ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- 10 i) methionine sulfoxide, or
- ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,
- 15 wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or
- 20 substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R³ and R⁴ are combined to form - (CH₂)_s - ;

25 R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- 30 i) methionine sulfoxide, or
- ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
- wherein the substituent is selected from F, Cl, Br, CF₃, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-,

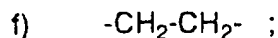
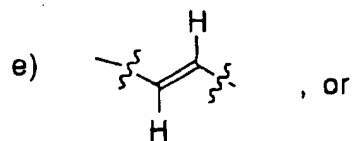
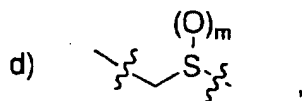
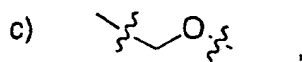
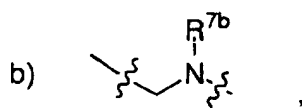
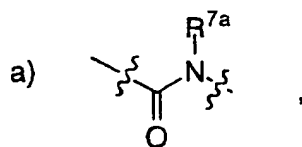
-26-

$R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$,
 $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and
 C_1-C_{20} alkyl,

- 5 d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O,
 10 $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$:

X-Y is



15 R^{7a} is selected from

-27-

- 5
- a) hydrogen,
 - b) unsubstituted or substituted aryl,
 - c) unsubstituted or substituted heterocycle,
 - d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
 - e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

R^{7b} is selected from

- 10
- a) hydrogen,
 - b) unsubstituted or substituted aryl,
 - c) unsubstituted or substituted heterocycle,
 - d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
 - e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl,
 - f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl, and
 - g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;
- 15
- 20
- 25

R⁸ is independently selected from:

- 30
- a) hydrogen,
 - b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

-28-

- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- 10 a) hydrogen,
 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 15 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from H, C₁-C₆ alkyl, benzyl, substituted aryl and C₁-C₆ alkyl substituted with substituted aryl;

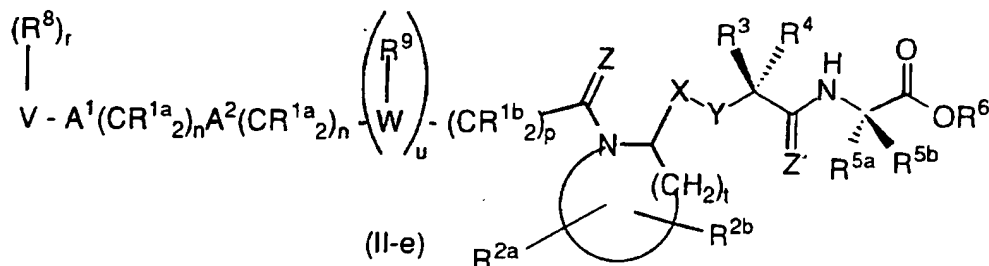
- 20 A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

- 25 Z is independently H₂ or O;

s is 4 or 5;
 t is 3, 4 or 5; and
 u is 0 or 1;

- 30 with respect to formula (II-e):

-29-



or a pharmaceutically acceptable salt thereof,

5 R^{11} , W , m , n , p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- 10 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- 15 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;

R^{2a} and R^{2b} are independently selected from:

- 20 a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N₃, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- 25 c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, $R^{10}O$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and

-30-

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

5 R³ and R⁴ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 10 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,
 wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 15 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
 and
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and
 20 C₃-C₁₀ cycloalkyl; or

R³ and R⁴ are combined to form - (CH₂)_s - ;

R^{5a} and R^{5b} are independently selected from:

- 25 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 30 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F, Cl, Br, CF₃, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,

-31-

$R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and
 C_1-C_{20} alkyl, and

- d) C_1-C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 C_3-C_{10} cycloalkyl; or

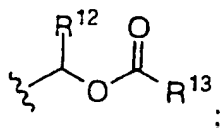
R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the
 carbon atoms is optionally replaced by a moiety selected from: O,
 $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$;

R^6 is

- a) substituted or unsubstituted C_1-C_8 alkyl, substituted or
 unsubstituted C_5-C_8 cycloalkyl, or substituted or
 unsubstituted cyclic amine, wherein the substituted alkyl,
 cycloalkyl or cyclic amine is substituted with 1 or 2
 substituents independently selected from:

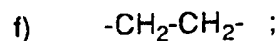
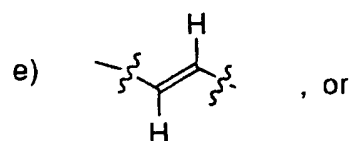
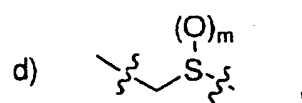
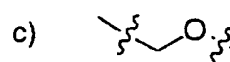
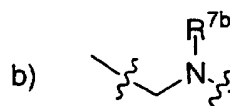
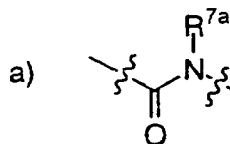
- 1) C_1-C_6 alkyl,
- 2) aryl,
- 3) heterocycle,
- 4) $-N(R^{11})_2$,
- 5) $-OR^{10}$, or

b)



$X-Y$ is

-32-



R7a is selected from

- 5 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
 10 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted
 or substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl;

R7b is selected from

- 15 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,

-33-

- 5 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl,
- f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl, and
- 10 g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

15 R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 25

R⁹ is selected from:

- a) hydrogen,
- 30 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

-34-

- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

5

R¹⁰ is independently selected from H, C₁-C₆ alkyl, benzyl, substituted aryl and C₁-C₆ alkyl substituted with substituted aryl;

R¹² is hydrogen or C₁-C₆ alkyl;

10

R¹³ is C₁-C₆ alkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-,

15

-N(R¹⁰)S(O)₂-, or S(O)_m;

Z is independently H₂ or O;

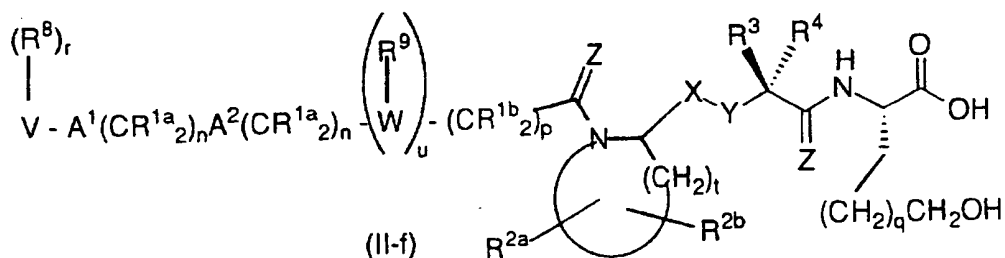
s is 4 or 5;

20

t is 3, 4 or 5; and

u is 0 or 1;

with respect to formula (II-f):



25

or a pharmaceutically acceptable salt thereof,

R¹¹, V, W, m, n, p and r are as defined above with respect to formula (II-a);

-35-

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂ or R¹¹OC(O)NR¹⁰-,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

R³ and R⁴ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,

-36-

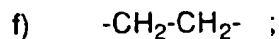
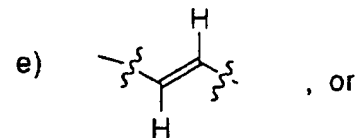
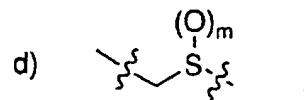
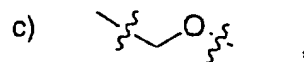
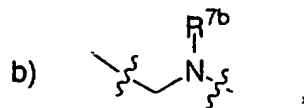
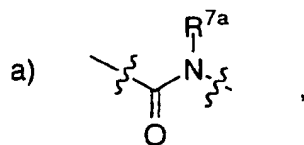
wherein the substituent is selected from F, Cl, Br,
 $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
 CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$,
 N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl,
 and

5

- d) C_1 - C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 C_3 - C_{10} cycloalkyl; or

10 R^3 and R^4 are combined to form $-(CH_2)_s-$;

X-Y is



R^{7a} is selected from

15

- a) hydrogen,

-37-

- 5
- b) unsubstituted or substituted aryl,
 - c) unsubstituted or substituted heterocycle,
 - d) unsubstituted or substituted C3-C10 cycloalkyl, and
 - e) C1-C6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C3-C10 cycloalkyl;

R7b is selected from

- 10
- a) hydrogen,
 - b) unsubstituted or substituted aryl,
 - c) unsubstituted or substituted heterocycle,
 - d) unsubstituted or substituted C3-C10 cycloalkyl,
 - e) C1-C6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C3-C10 cycloalkyl,
- 15
- f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C3-C10 cycloalkyl and C1-C6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C3-C10 cycloalkyl, and
- 20
- g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C3-C10 cycloalkyl and C1-C6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C3-C10 cycloalkyl;
- 25

R8 is independently selected from:

- 30
- a) hydrogen,
 - b) aryl, heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

-38-

- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from H, C₁-C₆ alkyl, benzyl, substituted aryl and C₁-C₆ alkyl substituted with substituted aryl;

R¹² is hydrogen or C₁-C₆ alkyl;

R¹³ is C₁-C₆ alkyl;

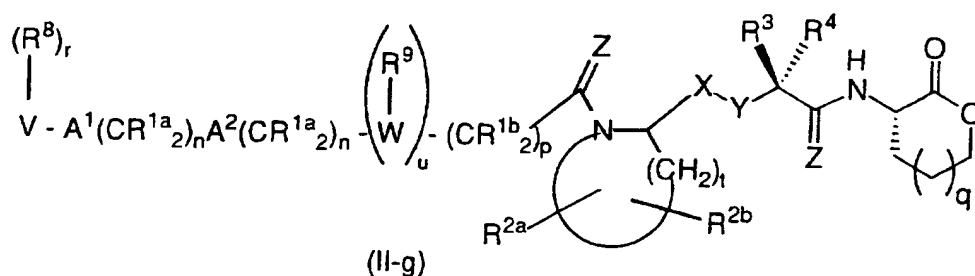
- A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

Z is independently H₂ or O;

- q is 0, 1 or 2;
 s is 4 or 5;
 t is 3, 4 or 5; and
 u is 0 or 1;

-39-

with respect to formula (II-g):



or a pharmaceutically acceptable salt thereof,

R^{11} , V , W , m , n , p and r are as previously defined with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N₃, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆

-40-

alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}-$, and

- d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3 - C_{10} cycloalkyl;

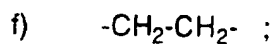
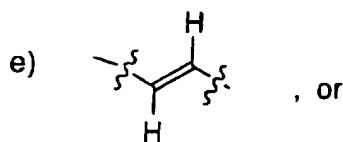
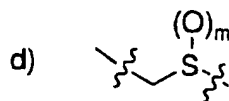
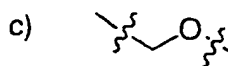
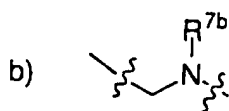
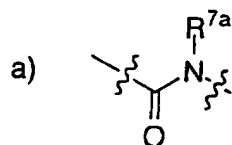
R^3 and R^4 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, C_3 - C_{10} cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F , Cl , Br , $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl,
 and
 d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3 - C_{10} cycloalkyl; or

R^3 and R^4 are combined to form $-(CH_2)_s-$;

-41-

X-Y is

R^{7a} is selected from

- a) hydrogen,
- 5 b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
- 10 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

R^{7b} is selected from

- a) hydrogen,
- 15 b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocycle.

-42-

- d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl,
- 5 f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl, and
- 10 g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

15

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 25

R⁹ is selected from:

- 30 a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

-43-

- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

5

R¹⁰ is independently selected from H, C₁-C₆ alkyl, benzyl, substituted aryl and C₁-C₆ alkyl substituted with substituted aryl;

R¹² is hydrogen or C₁-C₆ alkyl;

10

R¹³ is C₁-C₆ alkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-,

15 -N(R¹⁰)S(O)₂-, or S(O)_m;

Z is independently H₂ or O;

q is 0, 1 or 2;

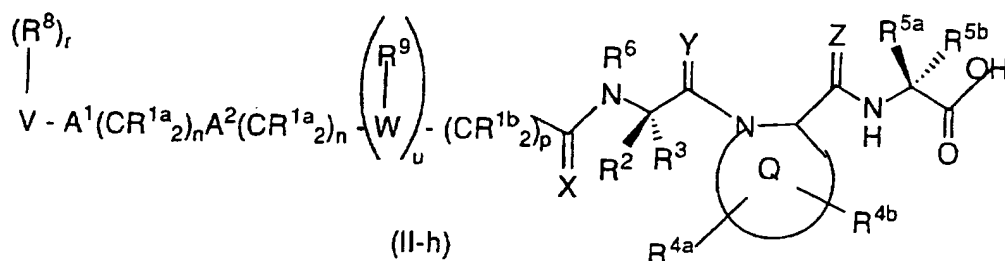
20 s is 4 or 5;

t is 3, 4 or 5; and

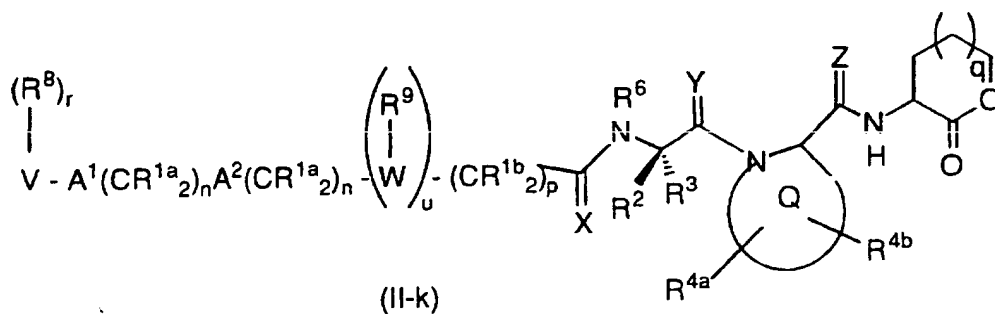
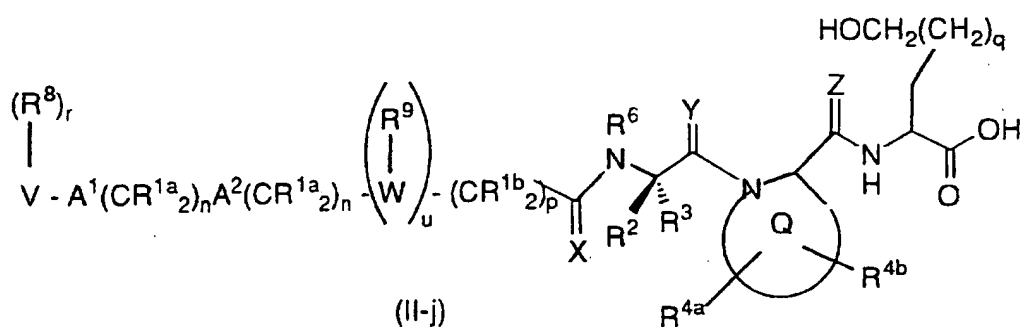
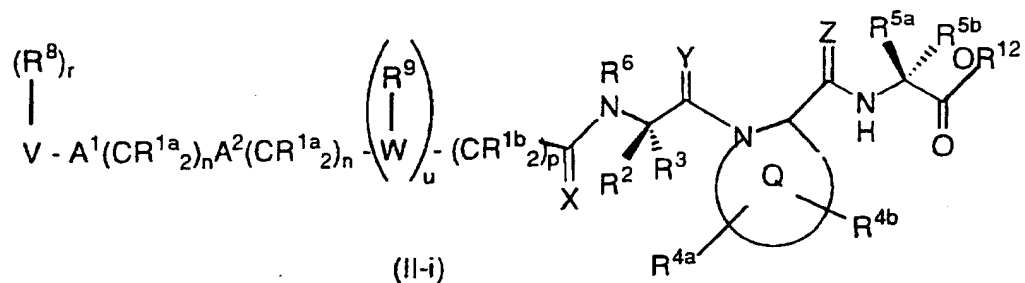
u is 0 or 1;

(c) a compound represented by formula (II-h) through (II-k):

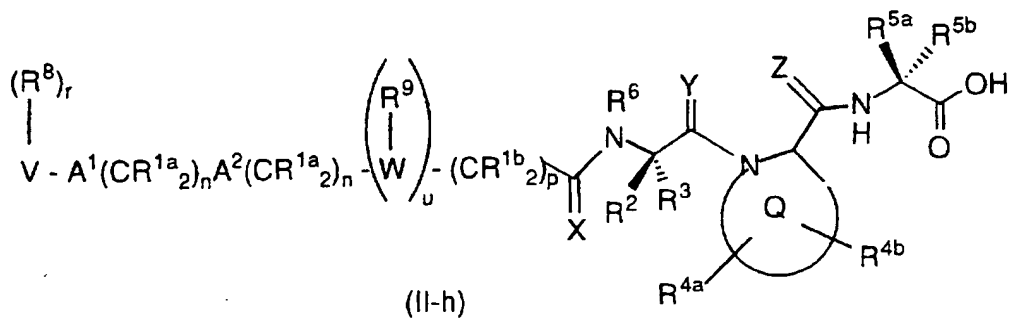
25



-44-



wherein with respect to formula (II-h):



or a pharmaceutically acceptable salt thereof,

-45-

R^{1a} , R^{1b} , R^8 , R^9 , R^{10} , R^{11} , A^1 , A^2 , V , W , m , n , p and r are as previously defined with respect to formula (II-a);

5 R^2 and R^3 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - 10 ii) methionine sulfone, and
- c) substituted or unsubstituted C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, C_3 - C_{10} cycloalkyl, aryl or heterocyclyl group,

wherein the substituent is selected from F, Cl, Br,

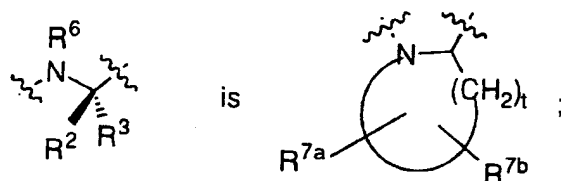
$N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,

15 CN , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl,

and
- d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and
- 20 C_3 - C_{10} cycloalkyl; or

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

25 R^2 or R^3 are combined with R^6 to form a ring such that



- R^{4a} , R^{4b} , R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,

-46-

- 5 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-,
R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-,
R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-,
10 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
(R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-,
N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or
substituted group selected from aryl, heterocyclyl and
10 C₃-C₁₀ cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- 15 b) an oxidized form of a side chain of a naturally occurring
amino acid which is:
- i) methionine sulfoxide, or
- ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl,
20 C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
wherein the substituent is selected from F, Cl, Br,
N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-,
N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
- d) C₁-C₆ alkyl substituted with an unsubstituted or
25 substituted group selected from aryl, heterocycle and
C₃-C₁₀ cycloalkyl; or

30 R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the
carbon atoms is optionally replaced by a moiety selected from: O,
S(O)_m, -NC(O)-, and -N(COR¹⁰)-;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

-47-

Q is a substituted or unsubstituted nitrogen-containing C4-C9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C5-C7 saturated ring or a heterocycle;

5 X, Y and Z are independently H₂ or O;

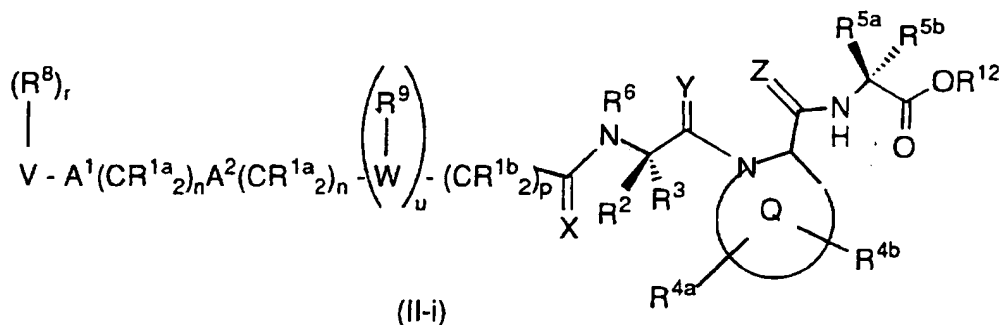
s is 4 or 5;

t is 3, 4 or 5; and

u is 0 or 1;

10

with respect to formula (II-i):



15 or a pharmaceutically acceptable salt thereof,
wherein:

R^{1a}, R^{1b}, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p and r are as
previously defined with respect to formula (II-a);

20

R² and R³ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,

25

-48-

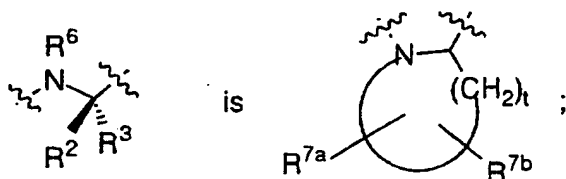
wherein the substituent is selected from F, Cl, Br,
 $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
 CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$,
 N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C₁-C₂₀ alkyl,
 and

5

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

10 R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^6 to form a ring such that



15

R^4a , R^4b , R^7a and R^7b are independently selected from:

- a) hydrogen,
 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, $R^{10}O-$,
 $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N_3 , $(R^{10})_2N-C(NR^{10})-$,
 $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
 20 c) aryl, heterocycle, cycloalkyl, alkenyl,
 $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 ,
 $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}-$, and
 25 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

R^5a and R^5b are independently selected from:

- 30 a) a side chain of a naturally occurring amino acid,

-49-

- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- i) methionine sulfoxide, or
 - ii) methionine sulfone,
- 5 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group, wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
- 10 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or
- 15 R^{5a} and R^{5b} are combined to form -(CH₂)_s- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)-;

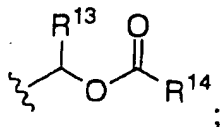
R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

20

R¹² is

- a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:
- 1) aryl,
 - 2) heterocycle,
 - 3) -N(R¹¹)₂,
 - 4) -OR¹⁰, or
- 25 b)

30



R¹³ is independently selected from hydrogen and C₁-C₆ alkyl;

-50-

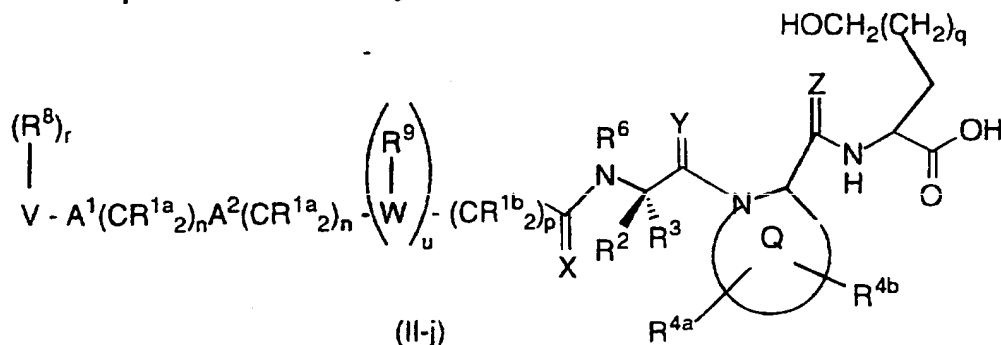
R^{14} is independently selected from C₁-C₆ alkyl;

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

X, Y and Z are independently H₂ or O;

s is 4 or 5;
 10 t is 3, 4 or 5; and
 u is 0 or 1;

with respect to formula (II-j):



15 or a pharmaceutically acceptable salt thereof,

R^{1a} , R^{1b} , R^8 , R^9 , R^{10} , R^{11} , A^1 , A^2 , V , W , m , n , p and r are as previously defined with respect to formula (II-a);

20 R^2 and R^3 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - 25 i) methionine sulfoxide, or
 - ii) methionine sulfone, and

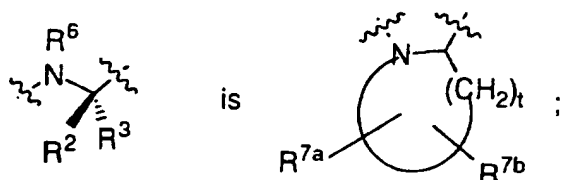
-51-

- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,
 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 5 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-,
 N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
 and
- d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 10 C₃-C₁₀ cycloalkyl; or

R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that

15



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
 20 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 c) aryl, heterocycle, cycloalkyl, alkenyl,
 25 R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂ or R¹¹OC(O)NR¹⁰-, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocyclyl and
 30 C₃-C₁₀ cycloalkyl;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

-52-

Q is a substituted or unsubstituted nitrogen-containing C4-C9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C5-C7 saturated ring or a heterocycle;

5

X, Y and Z are independently H₂ or O;

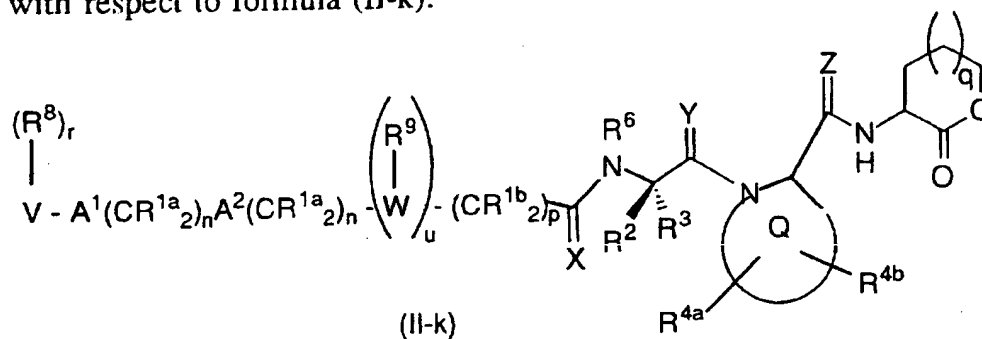
q is 0, 1 or 2;

s is 4 or 5;

10 t is 3, 4 or 5; and

u is 0 or 1;

with respect to formula (II-k):



15

or a pharmaceutically acceptable salt thereof,

R^{1a} , R^{1b} , R^8 , R^9 , R^{10} , R^{11} , A^1 , A^2 , V , W , m , n , p , and r are as defined above with respect to formula (II-a);

20

R^2 and R^3 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,

25

-53-

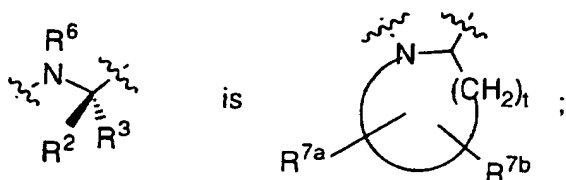
wherein the substituent is selected from F, Cl, Br,
 $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
 CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$,
 N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl,
 and

5

- d) C_1 - C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 C_3 - C_{10} cycloalkyl; or

10 R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^6 to form a ring such that



15

R^{4a} , R^{4b} , R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
 b) C_1 - C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O-$,
 $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N_3 , $(R^{10})_2N-C(NR^{10})-$,
 20 $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
 c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$,
 $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 ,
 $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$,
 N_3 , $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}-$, and
 25 d) C_1 - C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocyclyl and
 C_3 - C_{10} cycloalkyl;

30 R^6 is independently selected from hydrogen or C_1 - C_6 alkyl;

-54-

Q is a substituted or unsubstituted nitrogen-containing C4-C9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C5-C7 saturated ring or a heterocycle;

5 X, Y and Z are independently H2 or O;

q is 0, 1 or 2;

s is 4 or 5;

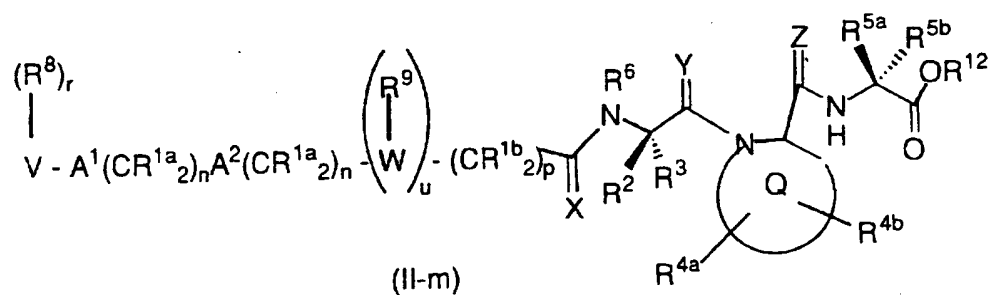
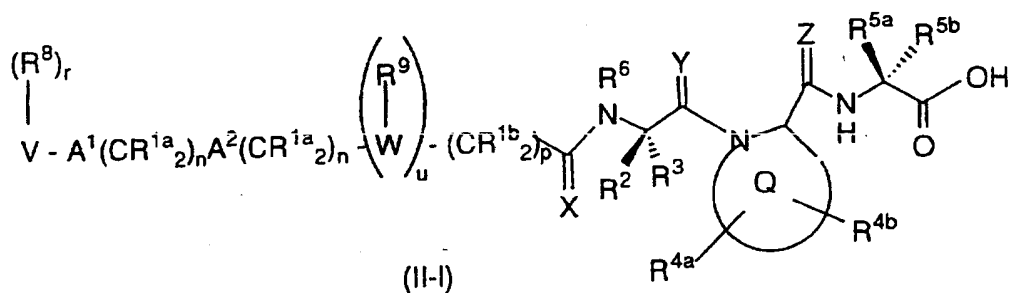
t is 3, 4 or 5; and

10 u is 0 or 1;

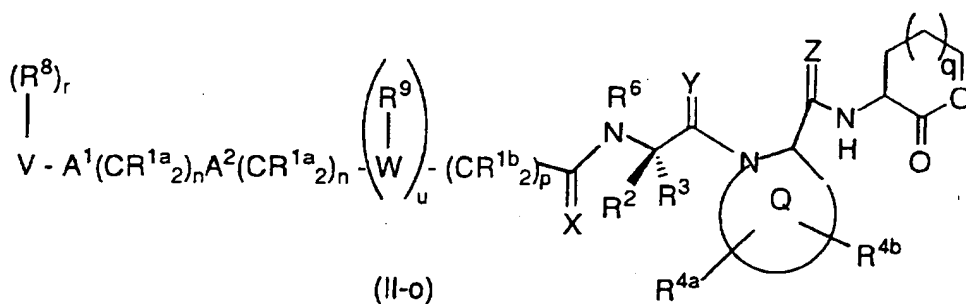
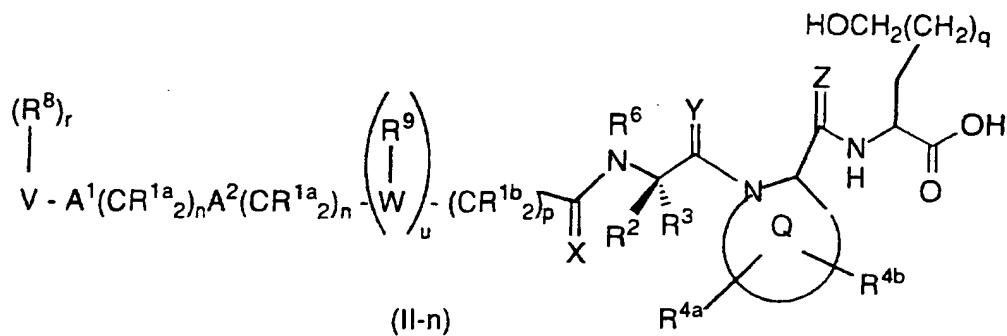
and

(d) a compound represented by formula (II-l) through (II-o):

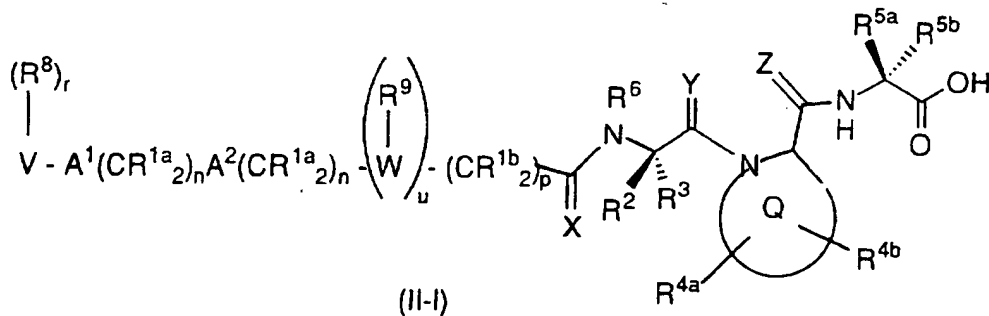
15



-55-



wherein with respect to formula (II-l):



5

or a pharmaceutically acceptable salt thereof:

R^{1a}, R^{1b}, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p and r are as defined above with respect to formula (II-a);

10

R² and R³ are independently selected from:

a) a side chain of a naturally occurring amino acid,

-56-

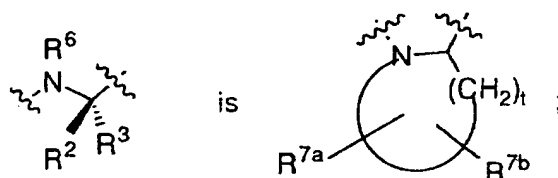
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- methionine sulfoxide, or
 - methionine sulfone, and
- 5 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,
- wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃-, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
- 10 and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

15

R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that

20



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- hydrogen,
- 25 C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 30 aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃-, -N(R¹⁰)₂ or R¹¹OC(O)NR¹⁰-, and

-57-

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

5 R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 10 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 15 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-,
 N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

20

R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

25 R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

30

X, Y and Z are independently H₂ or O;

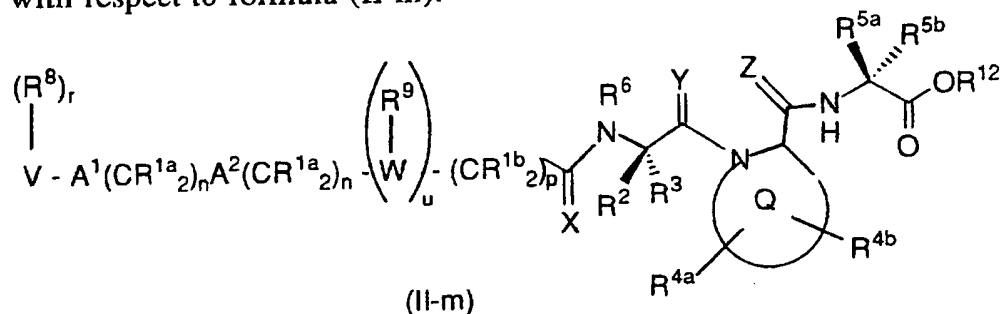
s is 4 or 5;

t is 3, 4 or 5; and

-58-

u is 0 or 1;

with respect to formula (II-m):



5 or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p and r are as defined above with respect to formula (II-a);

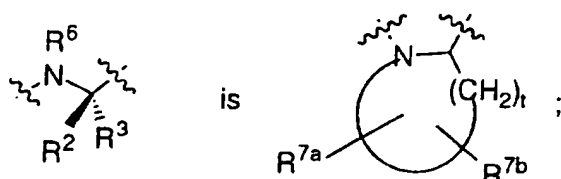
10 R2 and R3 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
i) methionine sulfoxide, or
ii) methionine sulfone, and
c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group, wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R² and R³ are combined to form - (CH₂)_s - ; or

-59-

R² or R³ are combined with R⁶ to form a ring such that



5 R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 10 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂ or R¹¹OC(O)NR¹⁰-, and
- 15 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- 20 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- 25 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,

-60-

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

10

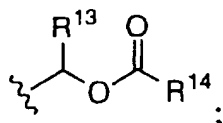
R¹² is

- a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:

15

- 1) aryl,
- 2) heterocycle,
- 3) -N(R¹¹)₂,
- 4) -OR¹⁰, or

b)



20

R¹³ is independently selected from hydrogen and C₁-C₆ alkyl;

R¹⁴ is independently selected from C₁-C₆ alkyl;

25

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

30 X, Y and Z are independently H₂ or O;

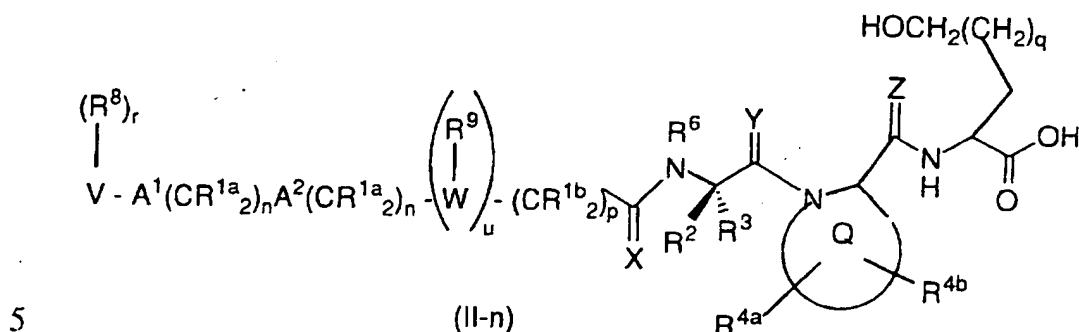
s is 4 or 5;

-61-

t is 3, 4 or 5; and

u is 0 or 1:

with respect to formula (II-n):



or a pharmaceutically acceptable salt thereof:

10 R^{1a}, R^{1b}, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p and r are as defined above with respect to formula (II-a);

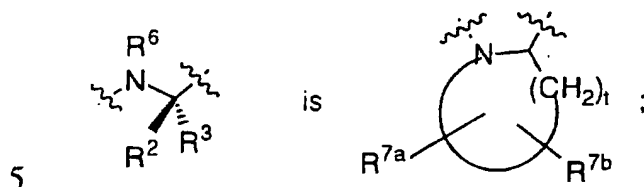
R2 and R3 are independently selected from:

- 15 a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
i) methionine sulfoxide, or
ii) methionine sulfone, and
c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,
20 wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
25 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

-62-

R² and R³ are combined to form $-(CH_2)_s-$; or

R² or R³ are combined with R⁶ to form a ring such that



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- 10
- a) hydrogen,
 - b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 - c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;
- 15

20 R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

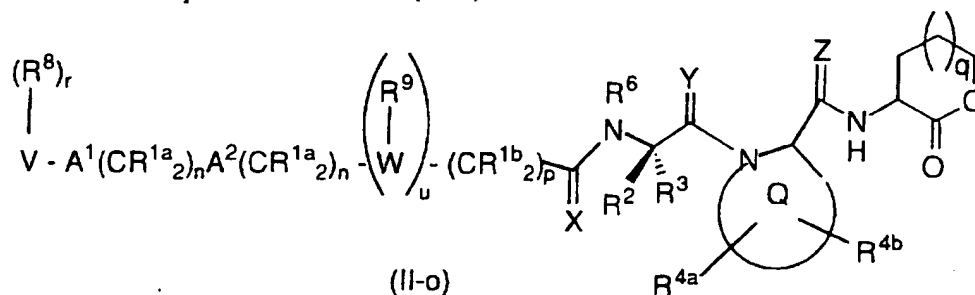
25

X, Y and Z are independently H₂ or O;

- 30
- q is 0, 1 or 2;
 - s is 4 or 5;
 - t is 3, 4 or 5; and
 - u is 0 or 1;

-63-

and with respect to formula (II-o):



5 or a pharmaceutically acceptable salt thereof:

R^{1a}, R^{1b}, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p and r are as defined above with respect to formula (II-a);

10 R² and R³ are independently selected from:

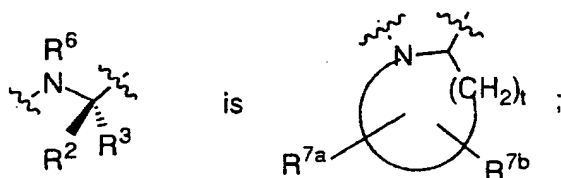
- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,

wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that

-64-



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- 5 a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 10 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂ or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and
- 15 C₃-C₁₀ cycloalkyl;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

20 Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

X, Y and Z are independently H₂ or O;

- 25 q is 0, 1 or 2;
- s is 4 or 5;
- t is 3, 4 or 5; and
- u is 0 or 1.

30 Specific compounds which antagonize Raf include the following:

-65-

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

5 4-[4-fluorophenyl)-3-pyridin-yl-1H-imidazol-2-yl]-1-acetyl-piperidine;

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

10 3-[4-fluorophenyl)-3-pyridin-yl-1H-imidazol-2-yl]-1-acetyl-piperidine;
and

4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester.

15 4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

20 4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-benzyl-piperidine;

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-ethyl-piperidine;

25 4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

30 2-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-butyl)-isoindole-1,3-dione;

2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-isoindole-1,3-dione;

-66-

2-(6-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-hexyl)-isoindole-1,3-dione;

5 4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-benzyl-piperidine;

10 2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-2,3-dihydro-isoindol-1-one ditrifluoroacetic acid salt;

4-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-ethyl)-pyridine;

15 2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-1,1-dioxobenzo[d]isothiazol-3-one;

20 2-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-butyl)-1,1-dioxobenzo[d]isothiazol-3-one;

2-amino-1-{5-[4-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-ethanone dihydrochloride;

25 4-[5-(3-hydroxyphenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

30 3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

-67-

- 4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1,4-dimethyl-piperidine;
- 5 4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;
- 4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;
- 10 4-{5-(3,4-dichlorophenyl)-2-[1-(2-phenylethyl)-piperidin-4-yl]-1H-imidazol-4-yl}-pyridine;
- 4-{5-(3,4-dichlorophenyl)-2-[1-(3-phenylpropyl)-piperidin-4-yl]-1H-imidazol-4-yl}-pyridine;
- 15 2-(6-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-hexyl)-1,1-dioxobenzo[d]isothiazol-3-one;
- 20 2-(3-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-propyl)-1,1-dioxobenzo[d]isothiazol-3-one;
- 4-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl-methyl}-imidazol-1-yl-methyl)-benzonitrile;
- 25 4-[2-[1-(4-benzyloxybenzyl)-piperidin-4-yl-5-(3,4-dichlorophenyl)-1H-imidazol-4-yl]-pyridine];
- 2-(3-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-propyl)-isoindole-1,3-dione;
- 30 4-[4-(4-fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzamidoxime;
- 4-(1-naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

-68-

- 4-(1-naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
- 4-(2-naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
- 5 4-(2-naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
- 4-(4-fluorophenyl)-2-(3-thiophenyl)-5-(4-pyridyl)imidazole;
- 4-(4-fluorophenyl)-2-(2-thiophenyl)-5-(4-pyridyl)imidazole;
- 10 4-(4-fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;
- 4-(4-fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
- 15 4-(4-fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
- 4-(4-fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)imidazole;
- 4-(4-fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
- 20 4-(4-fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
- 4-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole;
- 25 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-1-methyl-5-(4-pyridyl)
imidazole;
- 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
- 30 4-(4-fluorophenyl)-2-(4-methylthiophenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
- 4-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-1-(N-morpholino-

-69-

propyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-1-(methylthio-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;

5

4-(4-fluorophenyl)-1-(methylsulfinyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole; and

10 4-(4-fluorophenyl)-1-(methylsulfonyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole.

Examples of compounds which antagonize or inhibit farnesyl protein transferase include the following:

15 2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

20 2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;

1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;

25 1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

30

2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;

2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

35 2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;

-70-

- 1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;
- 5 1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;
- 2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;
- 10 1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 15 2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;
- 2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;
- 20 2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]acetyl]-4-(1-naphthoyl)piperazine;
- 2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)ethyl]-4-(1-naphthoyl)piperazine;
- 25 1-(2(R)-Amino-3-hydroxypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 30 1-(2-Amino-3-(2-benzoyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;
- 1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

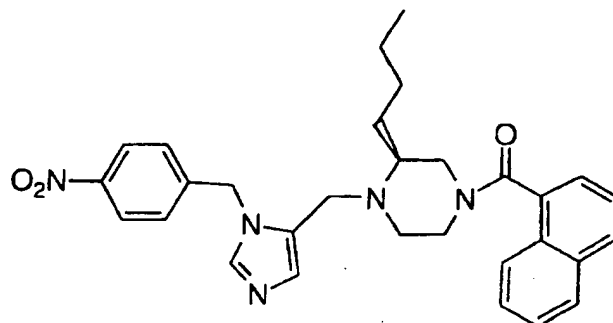
-71-

- 1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;
- 5 2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;
- 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;
- 10 1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;
- 15 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;
- 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;
- 20 2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;
- 25 2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;
- 2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;
- 30 2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

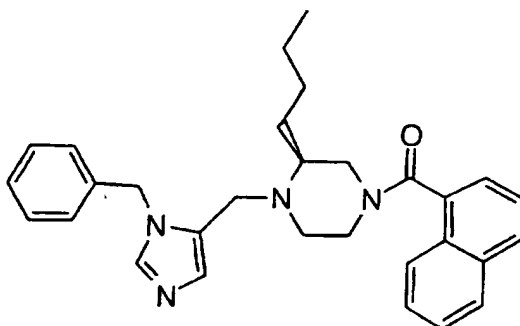
-72-

- 1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;
- 5 2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;
- 10 2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;
- 1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;
- 15 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;
- 20 1-[[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;
- 25 1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine

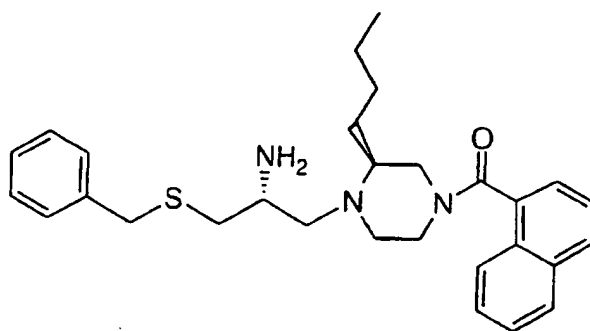
-73-



1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine

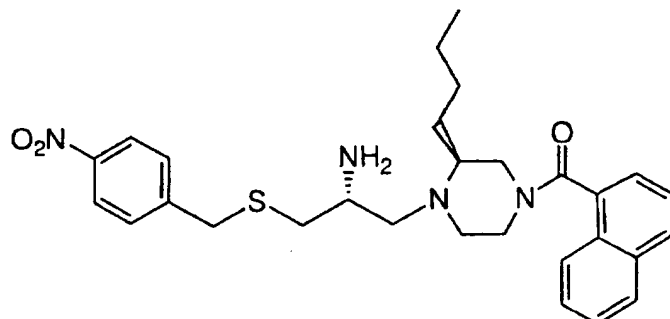


1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine

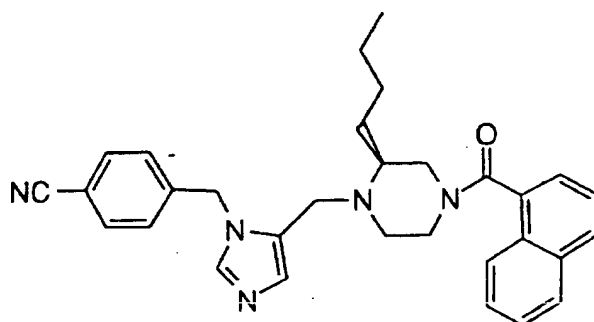


1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine

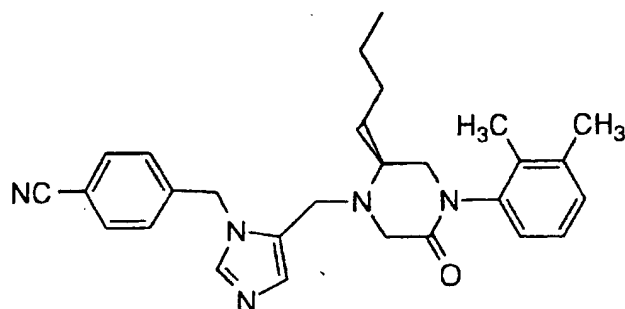
-74-



2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

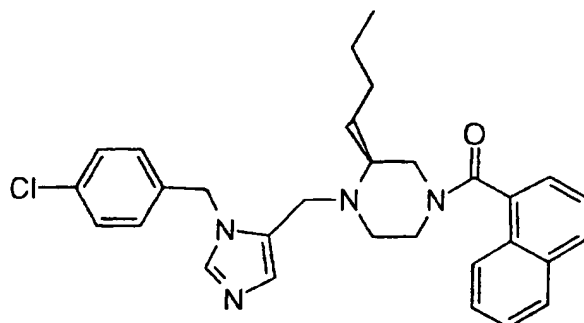


5 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one

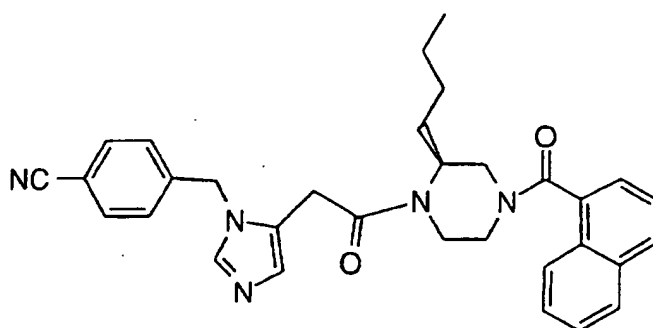


2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

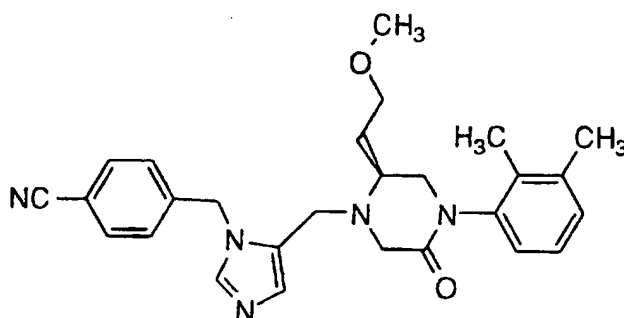
-75-



1-[[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine

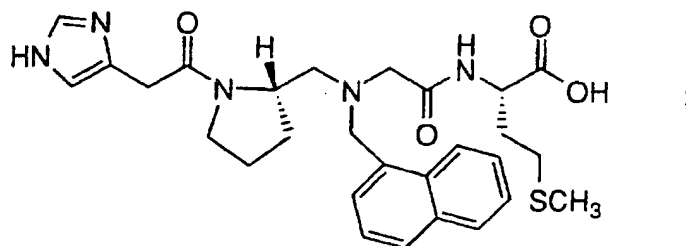


5 1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one



10 N-[1-(4-Imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycylmethionine

-76-



N-[1-(4-Imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

- 5 N-[1-(2(S),3-Diaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2(S),3-Diaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

10

N-[1-(3-Aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 15 N-[1-(3-Aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2(S)-Amino-3-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 20 N-[1-(2(S)-Amino-3-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

- 25 N-[1-(3-Amino-2(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-Amino-2(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

-77-

N-[1-(L-Glutaminyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 5 N-[1-(L-Glutaminyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-Histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ;

10

N-[1-(L-Histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

- 15 N-[1-(D-Histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(D-Histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

- 20 N-[1-(L-Pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(L-Pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

25

2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

- 30 2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine isopropyl ester;

-78-

2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

5 2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine sulfone;

10 2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine sulfone methyl ester;

15 2(S)-[1-(Pyrid-3-ylcarboxy)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(Pyrid-3-ylcarboxy)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

20 2(R)-{2-[1-(Naphth-2-yl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenylpropionyl-methionine;

2(R)-{2-[1-(Naphth-2-yl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenylpropionyl-methionine methyl ester;

25 2(S)-[1-(Pyrid-3-ylmethyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

30 2(S)-[1-(Pyrid-3-ylmethyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

-79-

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone isopropyl ester;

5 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

10 N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

15 N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone methyl ester ;

20 N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone;

N-[1-(Sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

25 N-[1-(Sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

30 N-[1-(N,N-Dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

N-[1-(N,N-Dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

-80-

- N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;
- 5 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;
- N-[1-(Glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;
- 10 N-[1-(Glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;
- N-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;
- 15 N-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;
- N-[1-(2-Acetylamino-3(S)-benzyloxycarbonylamino-3(S)-aminopropionyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;
- 20 N-[1-(2-Acetylamino-3(S)-aminopropionyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;
- 25 N-[1-(2-Amino-3(S)-acetylamino-3(S)-aminopropionyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;
- 30 2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy]-3-phenylpropionyl-methionine methyl ester;
- 2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy]-3-phenylpropionyl-methionine;

-81-

- 2(R)-{2-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester ;
- 5 2(R)-{2-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;
- 2(R)-{2-[1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;
- 10 2(R)-{2-[1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;
- 2(R)-{2-[1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;
- 15 2(R)-{2-[1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;
- 2(R)-{2-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;
- 20 2(R)-{2-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;
- 25 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine methyl ester;
- N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine;
- 30 N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine methyl ester;

-82-

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-
(β -acetyl amino)alanine;

5 N-[1-(Seryl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-
methionine methyl ester;

N-[1-(D-Alanyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-
methionine methyl ester;

10 N-[1-(1H-imidazol-4-carbonyl)pyrrolidin-2(S)-ylmethyl]- N-(1-
naphthylmethyl)glycyl-methionine methyl ester;

15 N-[1-(Isoasparagyl) pyrrolidin-2(S)-ylmethyl]-N-(1-
naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]- N-(1-
naphthylmethyl)glycyl-methionine methyl ester;

20 N-[1-(3-Pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-
naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2-Pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-
naphthylmethyl)glycyl-methionine methyl ester ;

25 N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-
naphthylmethyl)glycyl-methionine methyl ester;

30 N-[1-(Seryl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-
methionine;

N-[1-(D-Alanyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-
methionine;

35 N-[1-(1H-Imidazol-4-carbonyl)pyrrolidin-2(S)-ylmethyl]- N-(1-
naphthylmethyl)glycyl-methionine ;

-83-

N-[1-(Isoasparagyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

5 N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-Pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

10 N-[1-(2-Pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

15 N-[1-(1H-Imidazol-4-ylmethyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

20 N-[1-(2-Aminoethyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(2-thienyl)alanine;

25 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(trifluoromethyl)alanine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(2(S)-amino-4-acetylamino)butyric acid ;

30 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N,N-dimethyl)glutamine;

-84-

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

5 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-methoxybenzyl)glycyl-methionine;

10 N-[1-(Glycyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

15 N-((4-Imidazolyl)methyl-(2S)-pyrrolidinylmethyl)-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(2-thienyl)alanine methyl ester;

20

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N,N-dimethyl)glutamine methyl ester ;

25 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(trifluoromethyl)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(2(S)-amino-4-acetylamino)butyric acid methyl ester;

30

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

-85-

- N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(benzyl)glycyl-methionine methyl ester;
- 5 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(4-methoxybenzyl)glycyl-methionine methyl ester;
- N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(benzyl)glycyl-methionine methyl ester;
- 10 N-[1-(Glycyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(benzyl)glycyl-methionine methyl ester;
- N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;
- 15 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine cyclohexyl ester;
- N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine benzyl ester;
- 20 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ethyl ester;
- 25 N-[1-(Sarcosyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;
- N-[1-(N,N-Dimethylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;
- 30 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine (2-pyridylmethyl) ester;
- N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine (1-glyceryl) ester;
- 35

-86-

N-[1-L-Prolylpyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

5 N-[1-(L-Prolyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1-Morpholinoacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

10 N-[1-(1-Morpholinoacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-Piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

15 N-[1-(4-Piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

20 N-[1-(3-Piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-Piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

25 N-[1-(2-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

30 N-[1-(4-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

-87-

- N-[1-(4-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;
- 5 N-[1-(4-Pyridyl(N-methyl)glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;
- N-[1-(4-Pyridyl(N-methyl)glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;
- 10 N-[1-(1H-Imidazol-4-ylpropionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine;
- N-[1-(1H-Imidazol-4-ylpropionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine methyl ester;
- 15 N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine;
- N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine methyl ester;
- 20 N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine cyclohexyl ester;
- 25 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N-methyl)glutamine;
- N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N-methyl)glutamine methyl ester ;
- 30 N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -methylcarbonylamino)alanine;

-88-

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -methylcarbonylamino)alanine methyl ester;

5 N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -methylsulfonylamino)alanine;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -methylsulfonylamino)alanine methyl ester;

10 N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -propionylamino)alanine ;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -propionylamino)alanine methyl ester;

15

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -pyrrolidinon-1-ylamino)alanine;

20 N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -pyrrolidinon-1-ylamino)alanine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine;

25 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

30

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

-89-

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine;

5 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

10 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

15 N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

20 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-cyanobenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-cyanobenzyl)glycyl-methionine methyl ester ;

25 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-cyanobenzyl)glycyl-methionine;

30 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

-90-

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

5 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

10 N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methylbenzyl)glycyl-methionine;

15 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methylbenzyl)glycyl-methionine methyl ester;

20 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-trifluoromethylbenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-trifluoromethylbenzyl)glycyl-methionine methyl ester;

25 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylsulfonyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylsulfonyl)glycyl-methionine methyl ester;

30 N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 4-N-methylpiperidinyl ester;

-91-

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine tert-butyl ester;

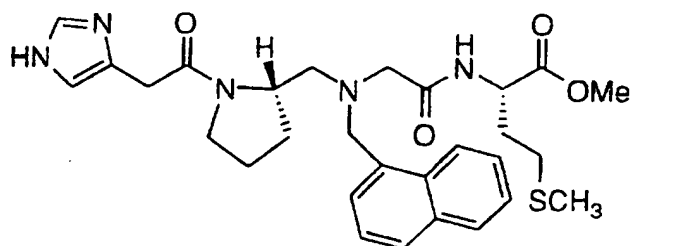
5 N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 3-pentyl ester;

N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

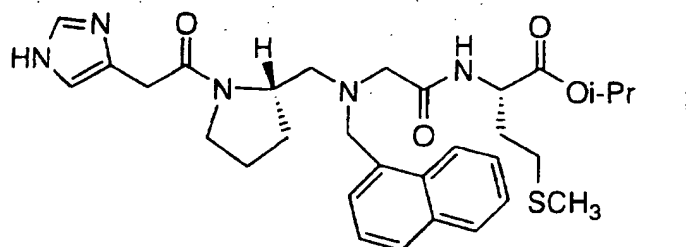
10 N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(4-Imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester

15

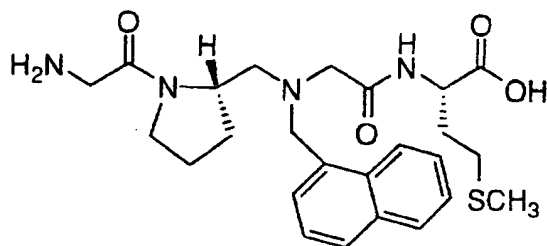


N-[1-(4-Imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester

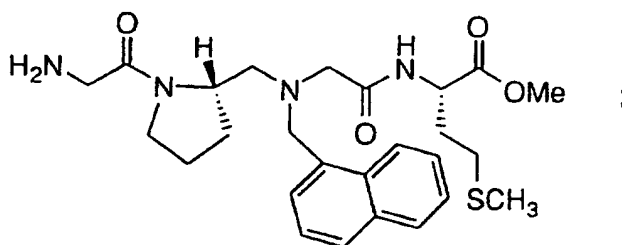


20 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine

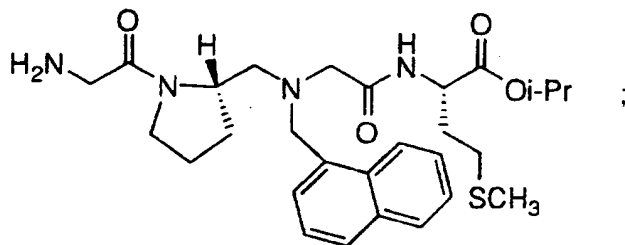
-92-



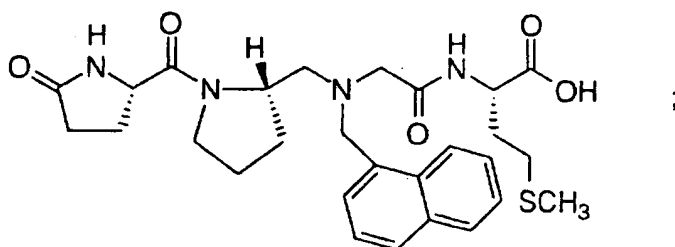
N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester



- 5 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester

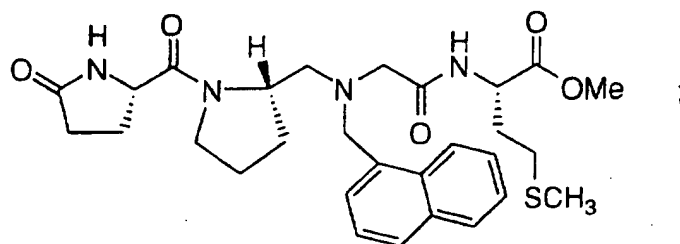


N-[1-(L-Pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine

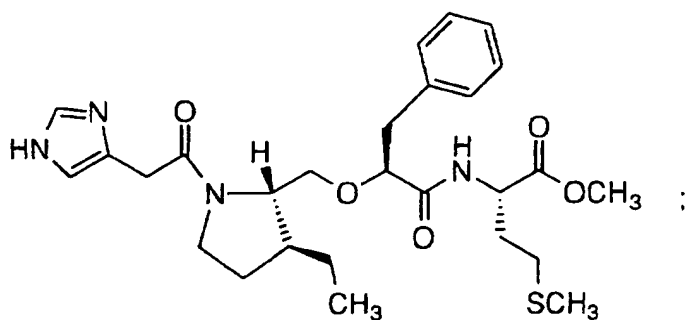


-93-

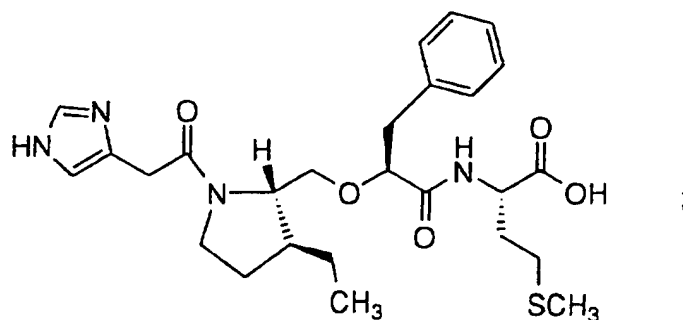
N-[1-(L-Pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester



2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy]-3-phenylpropionyl-methionine methyl ester

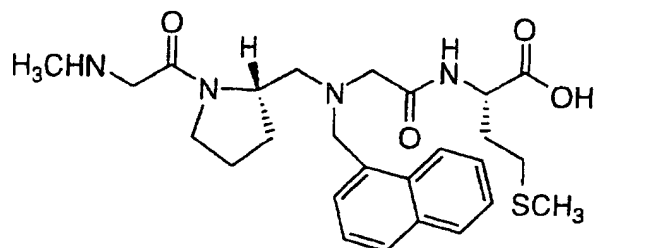


2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy]-3-phenylpropionyl-methionine

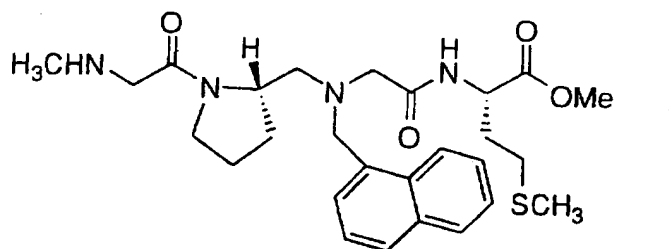


10 N-[1-(Sarcosyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine

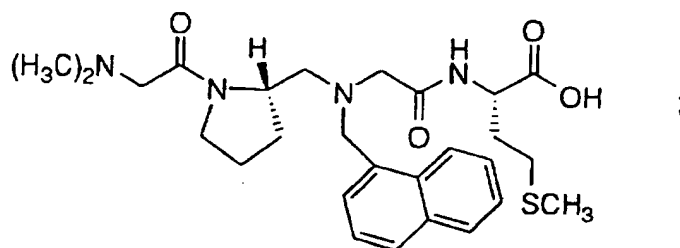
-94-



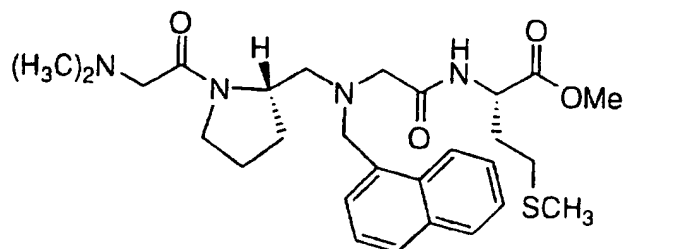
N-[1-(Sarcosyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester



- 5 N-[1-(N,N-Dimethylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine

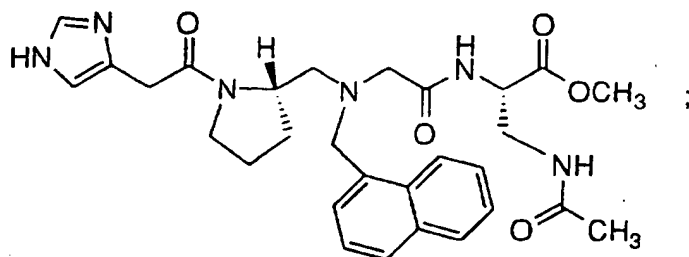


N-[1-(N,N-Dimethylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester

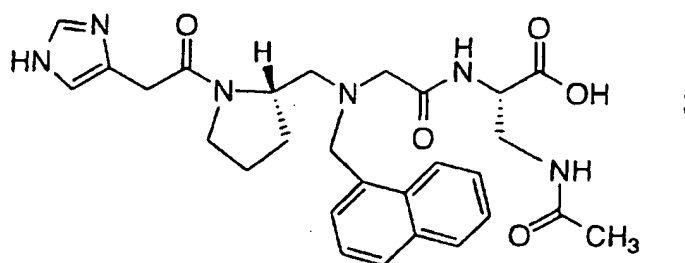


-95-

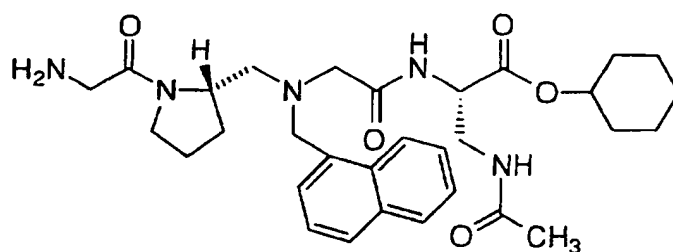
N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine methyl ester



5 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine

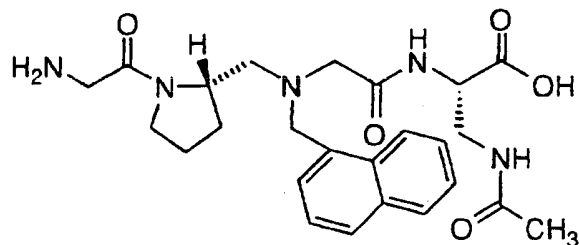


N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine cyclohexyl ester

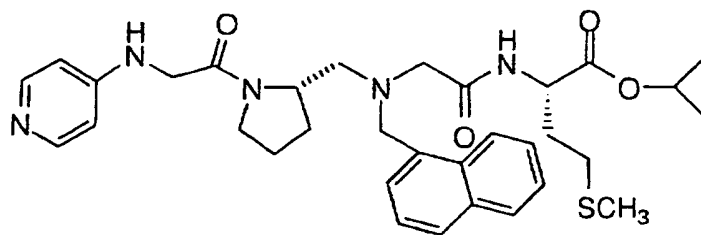


10 N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine

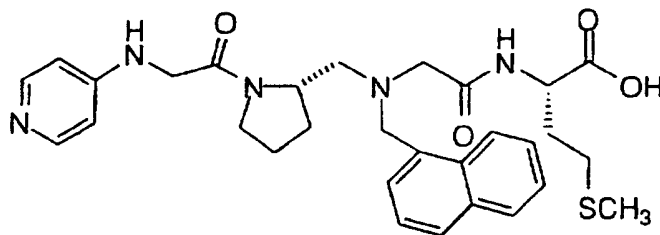
-96-



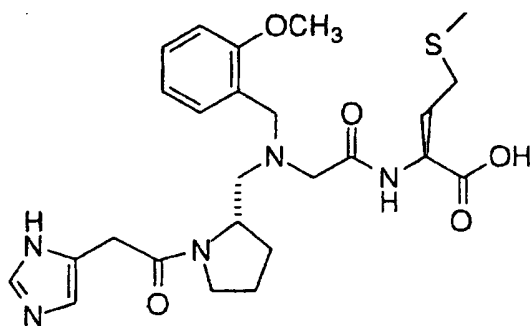
N-[1-(4-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester



- 5 N-[1-(4-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine

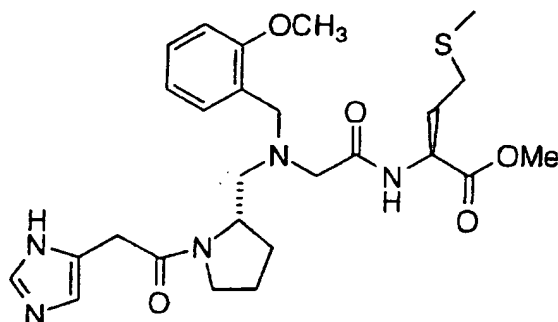


N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine

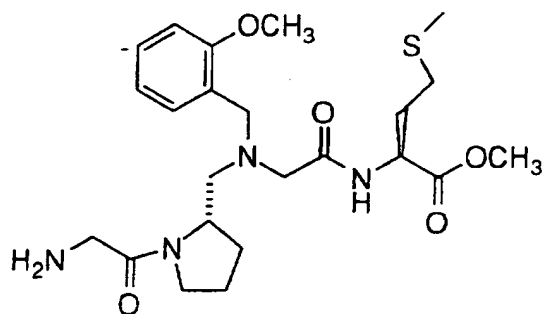


-97-

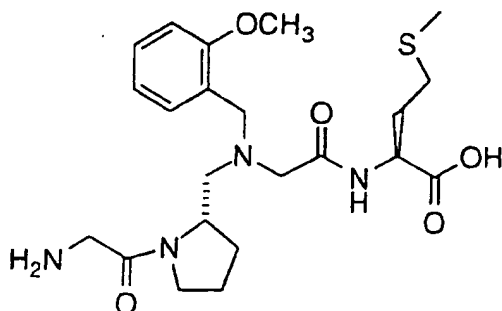
N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester



5 N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester

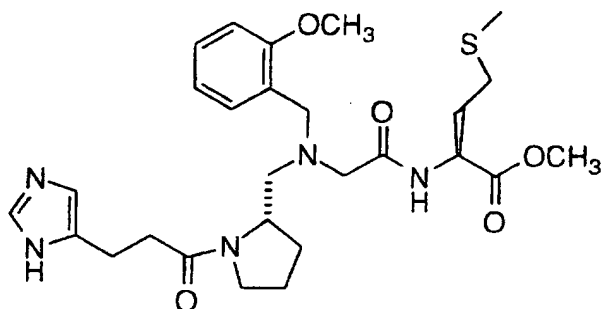


N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine

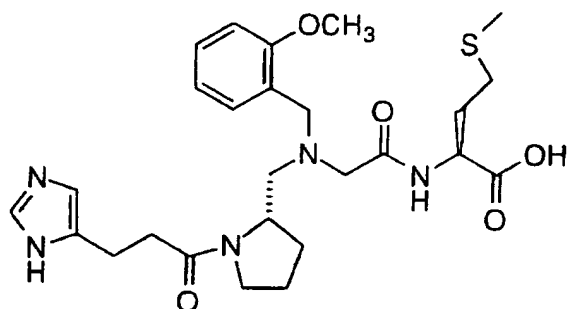


10 N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester

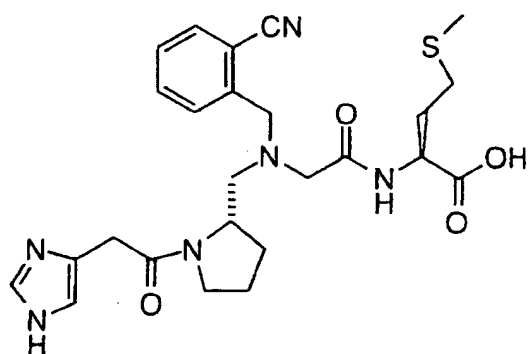
-98-



N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine

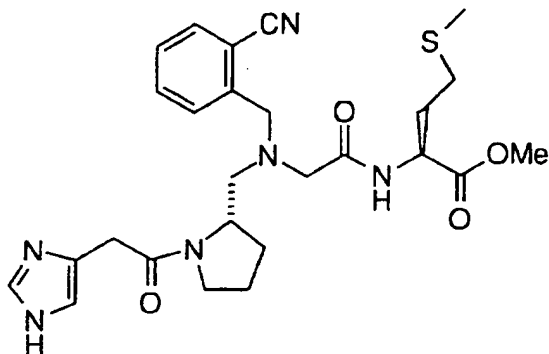


- 5 N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine

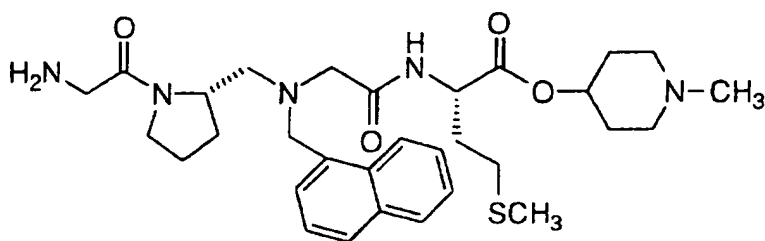


N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester

-99-

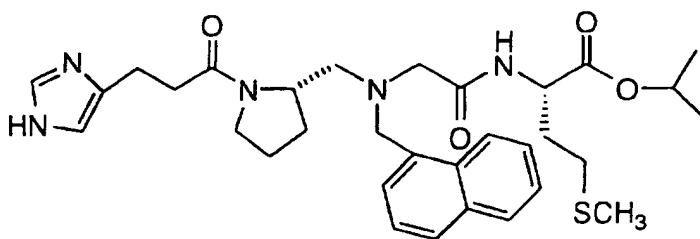


N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 4-N-methylpiperidinyl ester



5

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester



10

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester;

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine;

15

-100-

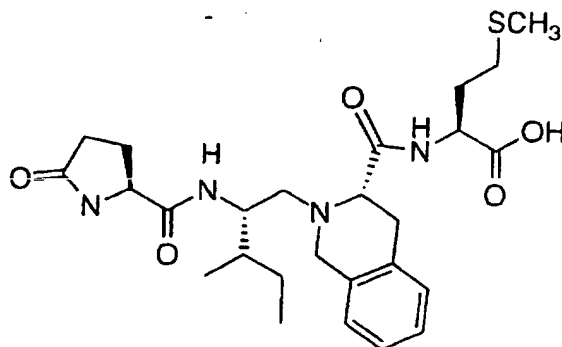
N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-
 prolyl-methionine methyl ester;

5 N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-
 prolyl-methionine;

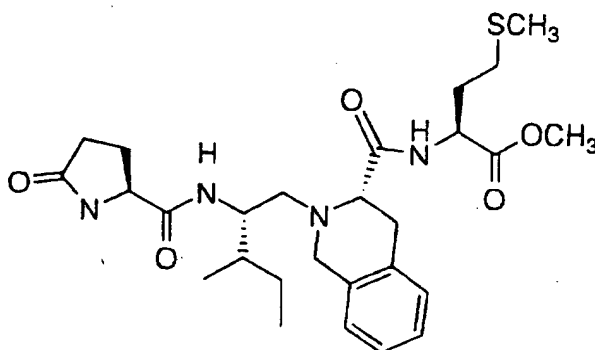
N-[1-Glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine
 methyl ester;

10 N-[1-Glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine;

N-[L-Pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-
 3(S)-isoquinolinecarbonyl-methionine

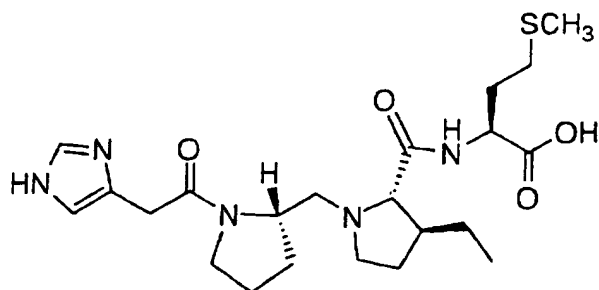


15 N-[L-Pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-
 3(S)-isoquinolinecarbonyl-methionine methyl ester

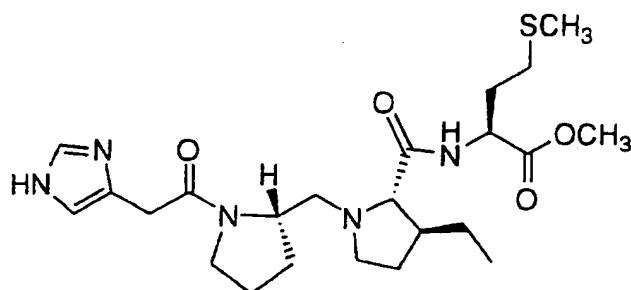


-101-

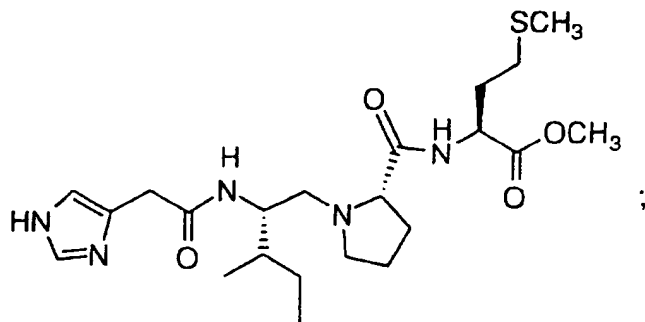
N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylproyl-methionine



5 N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylproyl-methionine methyl ester

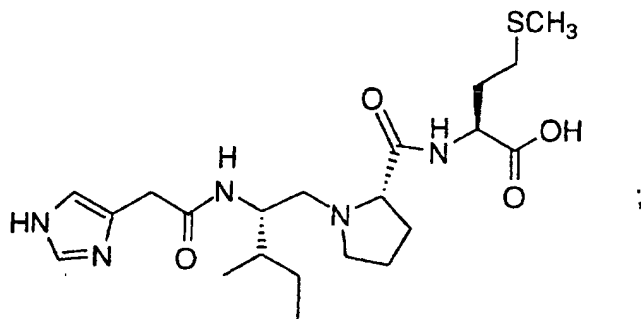


N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester



10 N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine

-102-



N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester

- 5 N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine

N-[L-Pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester

10

N-[L-Pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine

- 15 N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine

- 20 N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine

25

N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine methyl ester

-103-

N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylpropyl-methionine

- 5 N-[1-Glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylpropyl-methionine methyl ester

N-[1-Glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylpropyl-methionine
2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine

10

1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine

- 15 2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine

1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine

- 20 1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine

1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine

- 25 2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine

2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine

2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine

30

1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine

-104-

1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-
piperazine

5 2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine

1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-
naphthoyl)piperazine

10 1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-
naphthoyl)piperazine

2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine

15 2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]acetyl]-4-(1-
naphthoyl)piperazine

20 2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]ethyl]-4-(1-
naphthoyl)piperazine

1-(2(R)-Amino-3-hydroxypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine

25 1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine

1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-
naphthoyl)piperazine

30 1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-
naphthoyl)piperazine

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine

-105-

2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-
piperazin-5-one

5 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-
dimethylphenyl)piperazin-5-one

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-
2(S)-(2-methoxyethyl)piperazin-5-one

10 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-
ylmethyl]-piperazine

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-
ylmethyl]-piperazine

15 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine

20 2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine

2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine

25 2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine

2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-
naphthoyl)piperazine

30 1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-
naphthoyl)piperazine

-106-

- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine
- 5 2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine
- 2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine
- 10 1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine
- 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine
- 15 2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine
- 1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine
- 20 (N-[1-Cyanobenzyl)-1H-imidazol-5-yl]acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine
- (N-[1-Cyanobenzyl)-1H-imidazol-5-yl]acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine methyl ester
- 25 (N-[1-Cyanobenzyl)-1H-imidazol-5-yl]acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester
- N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester
- 30

Compounds which are useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications:

-107-

- USSN 60/005,059 filed on October 6, 1995;
USSN 60/005,063 filed on October 6, 1995
USSN 60/005,521 filed on October 13, 1995
WO 95/32987 published on 7 December 1995.
- 5 U. S. Pat. No. 5,420,245;
European Pat. Publ. 0 618 221 ;
WO 94/26723;
WO 95/08542 ;
WO 95/11917;
- 10 WO 95/12612.
- U. S. Pat. No. 5,238,922 granted on August 24, 1993; ;
- 15 U. S. Pat. No. 5,340,828 granted on August 23, 1994; ;
- U. S. Pat. No. 5,352,705 granted on October 4, 1994;
- U. S. Pat. No. 5,326,773 granted on July 5, 1994;
- 20 USSN 07/968,022 filed on October 29, 1992 ;
- USSN 08/968,025 filed on October 29, 1992 and USSN 08/143,943 filed
on October 27, 1993 ;
- 25 USSN 08/080,028 filed on June 18, 1993 and USSN 08/237,586 filed on
May 11, 1994 ;
- USSN 08/314,987 filed on September 29, 1994
- 30 USSN 08/315,171 filed on September 29, 1994
- USSN 08/315,046 filed on September 29, 1994 ;
- 35 USSN 08/315,161 filed on September 29, 1994; USSN 08/399,282 filed
on March 6, 1995; USSN 472,077 filed on June 6, 1995 and USSN
08/527,972 filed on September 14, 1995

-108-

USSN 08/315,151 filed on September 29, 1994 ;

USSN 08/314,974 filed on September 29, 1994

5

USSN 08/412,621 filed on March 29, 1995 and USSN 08/448,865 filed on May 24, 1995 ;

USSN 08/413,137 filed on March 29, 1995; ;

10

USSN 08/412,828 filed on March 29, 1995;

USSN 08/412,829 filed on March 29, 1995; and USSN 08/470,690 filed on June 6, 1995;

15

USSN 08/412,830 filed on March 29, 1995;

USSN 08/449,038 filed on May 24, 1995; ;

20 USSN 08/468,160 filed on June 6, 1995; ;

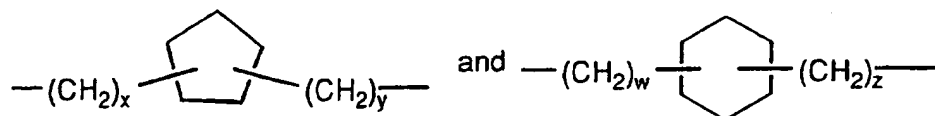
All patents, publications and pending patent applications identified are hereby incorporated by reference.

25 The Raf antagonists are described herein using the terms defined below unless otherwise specified.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, 30 propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

- Alkyl also includes a straight or branched alkyl group which contains or is interrupted by a cycloalkylene portion. Examples include the following:

-109-



wherein: x and y = from 0-10; and w and z = from 0-9.

The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

Heteroalkyl refers to an alkyl group having from 2-15 carbon atoms, and interrupted by from 1-4 heteroatoms selected from O, S and N.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted

-110-

when a substituted alkynyl group is provided.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups. With regard to the farnesyl transferase inhibitors, "aryl" is intended to include any stable monocyclic, bicyclic or tricyclic carbon ring(s) of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include phenyl, naphthyl, anthracenyl, biphenyl, tetrahydronaphthyl, indanyl, phenanthrenyl and the like.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type are thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole, oxazine, pyrazole, tetrazole, imidazole, pyridine, pyrimidine, pyrazine and triazine. Examples of partially aromatic groups are tetrahydro-imidazo[4,5-c]pyridine, phthalidyl and saccharinyl, as defined below.

With regard to the farnesyl transferase inhibitors, the term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocycle ring which is either saturated or

-111-

unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydro-benzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazoliny, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, pyridonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolinyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Preferably, heterocycle is selected from imidazolyl, 2-oxopyrrolidinyl, piperidyl, pyridyl and pyrrolidinyl.

Substituted alkyl, aryl and heteroaryl, and the substituted portions of aralkyl, aralkoxy, heteroaralkyl, heteroaralkoxy and like groups are substituted with from 1-3 groups selected from the group consisting of: halo, hydroxy, cyano, acyl, acylamino, aralkoxy, alkylsulfonyl, arylsulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, alkyl, alkoxy, aryl, aryloxy, aralkoxy, amino, alkylamino, dialkylamino, and sulfonylamino.

With regard to the farnesyl transferase inhibitors, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or

-112-

2 substituents selected from the group which includes but is not limited to F, Cl, Br, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, CN, (C₁-C₆ alkyl)O-, -OH, (C₁-C₆ alkyl)S(O)_m-, (C₁-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, (C₁-C₆ alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, N₃, (C₁-C₆ alkyl)OC(O)NH- and C₁-C₂₀ alkyl.

The terms "heterocycloalkyl" and "heterocyclyl" refer to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S(O)_y or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms. When three heteroatoms are present in the heterocycle, they are not all linked together.

Examples of heterocyclyls are piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, imidazolyl, piperazinyl, pyrrolidine-2-one, piperidine-2-one and the like.

Acyl as used herein refers to -C(O)C₁₋₆ alkyl and -C(O)-aryl.

Acylamino refers to the group -NHC(O)C₁₋₆ alkyl and -NHC(O)aryl.

Aralkoxy refers to the group -OC₁₋₆ alkylaryl.

Alkylsulfonyl refers to the group -SO₂C₁₋₆ alkyl.

Alkylsulfonylamino refers to the group -NHSO₂C₁₋₆alkyl.

Arylsulfonylamino refers to the group -NHSO₂aryl.

Alkylaminocarbonyl refers to the group -C(O)NHC₁₋₆alkyl.

Aryloxy refers to the group -O-aryl.

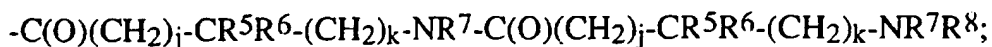
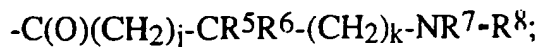
Aralkoxy refers to the group -O-C₁₋₆ alkylaryl.

Sulfonylamino refers to the group -NHSO₃H.

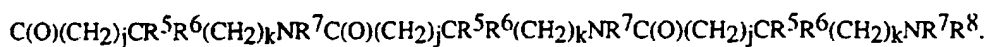
Halo means Cl, F, Br and I selected on an independent basis.

Within $-\left[\text{C}(\text{O})(\text{CH}_2)_j\text{-CR}^5\text{R}^6\text{-(CH}_2)_k\text{-NR}^7\right]_p\text{-R}^8$, there may be from 1 to 3 groups $-\left[\text{C}(\text{O})(\text{CH}_2)_j\text{-CR}^5\text{R}^6\text{-(CH}_2)_k\text{-NR}^7\right]-$. Thus, $-\left[\text{C}(\text{O})(\text{CH}_2)_j\text{-CR}^5\text{R}^6\text{-(CH}_2)_k\text{-NR}^7\right]_p\text{-R}^8$ with p equal to 1, 2 or 3 means the following:

-113-

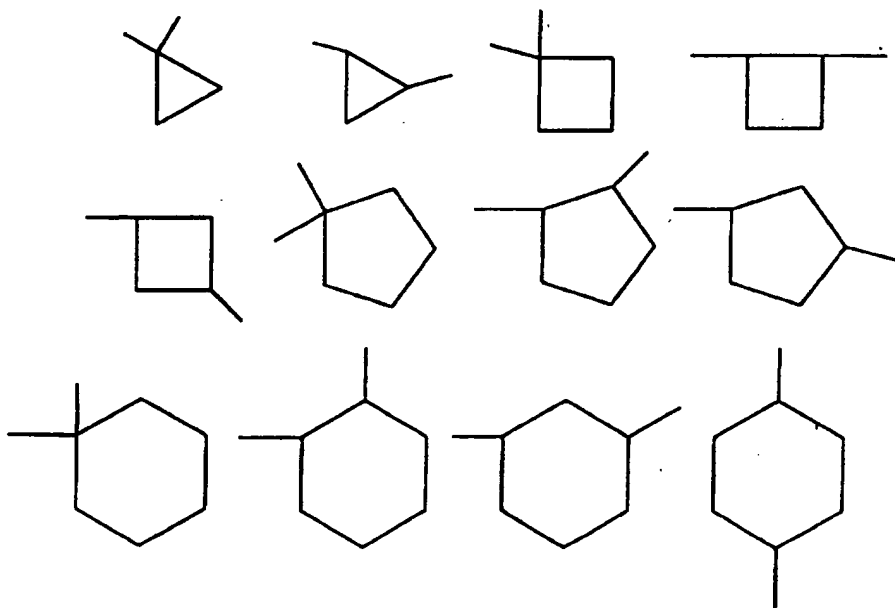


5 and



10 Within these groups, the variables are determined independently. For example, when more than one j is present, they may be the same or different. When CR^5R^6 is taken in combination, it represents a 3, 4, 5 or 6 membered cycloalkyl or heterocyclyl group, an aryl group or a heteroaryl group. Examples of suitable cycloalkylene attachment are as follows:

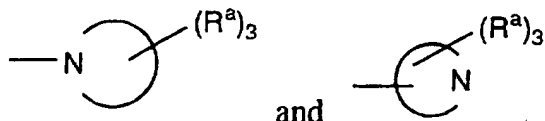
15



In each of the patterns of attachment noted above, the ring may also be heterocyclic as defined above.

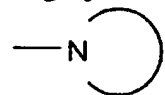
20

-114-



are optional substituents linked to the HETCy group.

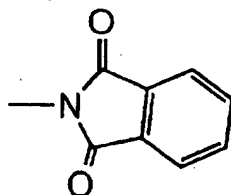
- 5 and independently represent mono or bicyclic ring systems, non-aromatic or partially aromatic, containing from 5-10 ring atoms, 1-4 of which are N and 0-1 of which are O or S(O)_y, with y equal to 0, 1 or 2, and when partially aromatic, the non-aromatic portion thereof optionally containing 1-2 carbonyl groups. Hence, these
10 ring systems can be heteroaryl or heterocyclic as defined above.



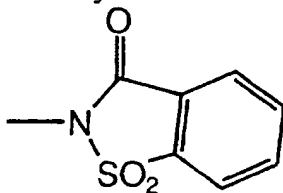
is linked to HETCy through a nitrogen atom contained in the ring system, either directly or through a linking group which is part of R'. Examples include phthalidyl and saccharinyl, as further defined below.

- 15 is likewise linked to HETCy, but through a carbon atom contained in the ring system.

The term phthalidyl refers to the heteroaryl group:



The term saccharinyl refers to the heteroaryl group:



-115-

In the present method, amino acids which are disclosed are identified both by conventional 3 letter and single letter abbreviations as indicated below:

5	Alanine	Ala	A
	Arginine	Arg	R
	Asparagine	Asn	N
	Aspartic acid	Asp	D
	Asparagine or		
10	Aspartic acid	Asx	B
	Cysteine	Cys	C
	Glutamine	Gln	Q
	Glutamic acid	Glu	E
	Glutamine or		
15	Glutamic acid	Glx	Z
	Glycine	Gly	G
	Histidine	His	H
	Isoleucine	Ile	I
	Leucine	Leu	L
20	Lysine	Lys	K
	Methionine	Met	M
	Phenylalanine	Phe	F
	Proline	Pro	P
	Serine	Ser	S
25	Threonine	Thr	T
	Tryptophan	Trp	W
	Tyrosine	Tyr	Y
	Valine	Val	V

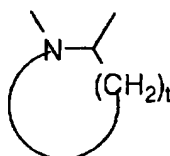
30

The compounds used in the present method may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. Unless otherwise

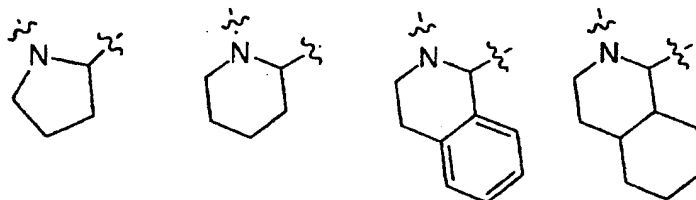
-116-

specified, named amino acids are understood to have the natural "L" stereoconfiguration

The following structure:



- 5 represents a cyclic amine moiety having 5 or 6 members in the ring, such a cyclic amine which may be optionally fused to a phenyl or cyclohexyl ring. Examples of such a cyclic amine moiety include, but are not limited to, the following specific structures:



- 10 It is also understood that substitution on the cyclic amine moiety by R^{2a} and R^{2b} may be on different carbon atoms or on the same carbon atom. When R^3 and R^4 are combined to form $-(CH_2)_s-$, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

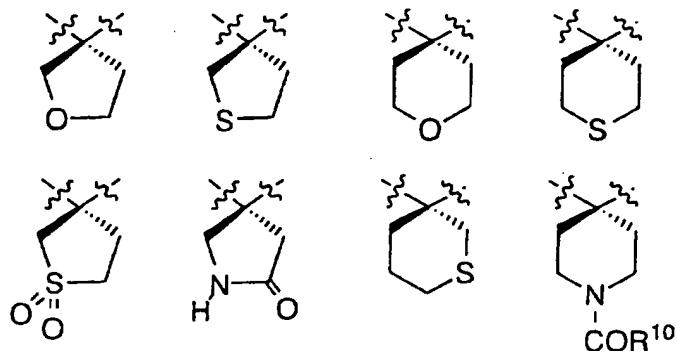


15

When R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$, cyclic moieties as described hereinabove for R^3 and R^4 are formed. In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:

20

-117-



The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{10} , Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents $-NHH$, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth below.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt-

-118-

forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

The compounds of formulas (II-a) through (II-k) can be synthesized from their constituent amino acids by conventional peptide synthesis techniques, and the additional methods described below. Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, "The Peptides", Vol. I, Academic Press 1965, or Bodanszky *et al.*, "Peptide Synthesis", Interscience Publishers, 1966, or McOmie (ed.) "Protective Groups in Organic Chemistry", Plenum Press, 1973, or Barany *et al.*, "The Peptides: Analysis, Synthesis, Biology" 2, Chapter 1, Academic Press, 1980, or Stewart *et al.*, "Solid Phase Peptide Synthesis", Second Edition, Pierce Chemical Company, 1984. Also useful in exemplifying syntheses of specific unnatural amino acid residues are European Pat. Appl. No. 0 350 163 A2 (particularly page 51-52) and J. E. Baldwin *et al.* *Tetrahedron*, 50:5049-5066 (1994). With regards to the synthesis of instant compounds containing a (β -acetylamino)alanine residue at the C-terminus, use of the commercially available N_{α} -Z-L-2,3-diaminopropionic acid (Fluka) as a starting material is preferred.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

Ac ₂ O	Acetic anhydride;
Boc	t-Butoxycarbonyl;
25 DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
DMAP	4-Dimethylaminopyridine;
DME	1,2-Dimethoxyethane;
DMF	Dimethylformamide;
EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-
30	hydrochloride;
HOBT	1-Hydroxybenzotriazole hydrate;
Et ₃ N	Triethylamine;
EtOAc	Ethyl acetate;
FAB	Fast atom bombardment;

-119-

	HOObt	3-Hydroxy-1,2,2-benzotriazin-4(3H)-one;
	HPLC	High-performance liquid chromatography;
	MCPBA	m-Chloroperoxybenzoic acid;
	MsCl	Methanesulfonyl chloride;
5	NaHMDS	Sodium bis(trimethylsilyl)amide;
	Py	Pyridine;
	TFA	Trifluoroacetic acid;
	THF	Tetrahydrofuran.

10 The compounds of formula (I-a) and (I-b) are prepared in accordance with U. S. Application No. 60/005,059 filed on October 6, 1995 and 60/005,063 filed on October 6, 1995. Two general methods for preparation of the imidazole nucleus are outlined. In the first, a suitably protected picolyl alcohol is deprotonated with
15 a strong base such as n-butyl lithium or lithium diisopropyl amide and the resulting anion is reacted with an appropriate N,O-dimethylhydrox-amide to give a protected alpha hydroxy ketone. The protected alpha hydroxy ketone is then condensed with a suitably functionalized and protected aminoaldehyde in the presence of ammonium acetate, acetic
20 acid and copper acetate.

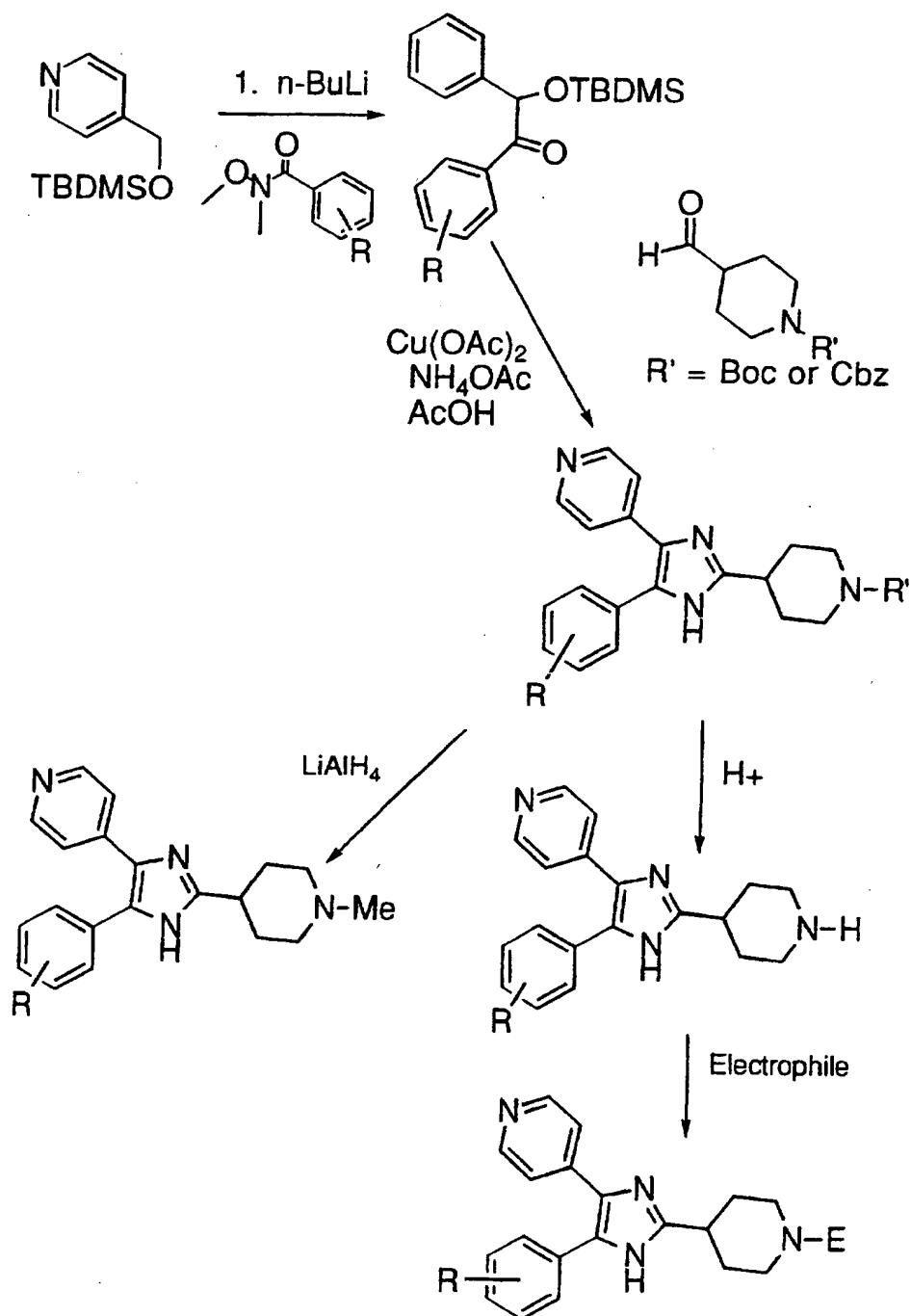
 The aldehydes typically used contain a suitably protected nitrogen atom. After the imidazole nucleus has been formed, the nitrogen is deprotected and then reacted with an appropriate electrophilic reagent to provide the final compounds.

25 In the second method, a suitably protected picolyl alcohol is deprotonated with a strong base such as n-butyl lithium or lithium diisopropyl amide and the resulting anion is reacted with an appropriate aryl or alkyl aldehyde to give a mono-protected diol. The protecting group is removed and the resulting diol is oxidized (by the method
30 of Swern or Moffat) to a dione. The dione is then condensed with a suitably functionalized and protected aminoaldehyde in the presence of ammonium acetate in acetic acid to give the imidazole.

 In this same manner, the nitrogen is deprotected and then reacted with an appropriate electrophilic reagent to provide the
35 compounds of formula I.

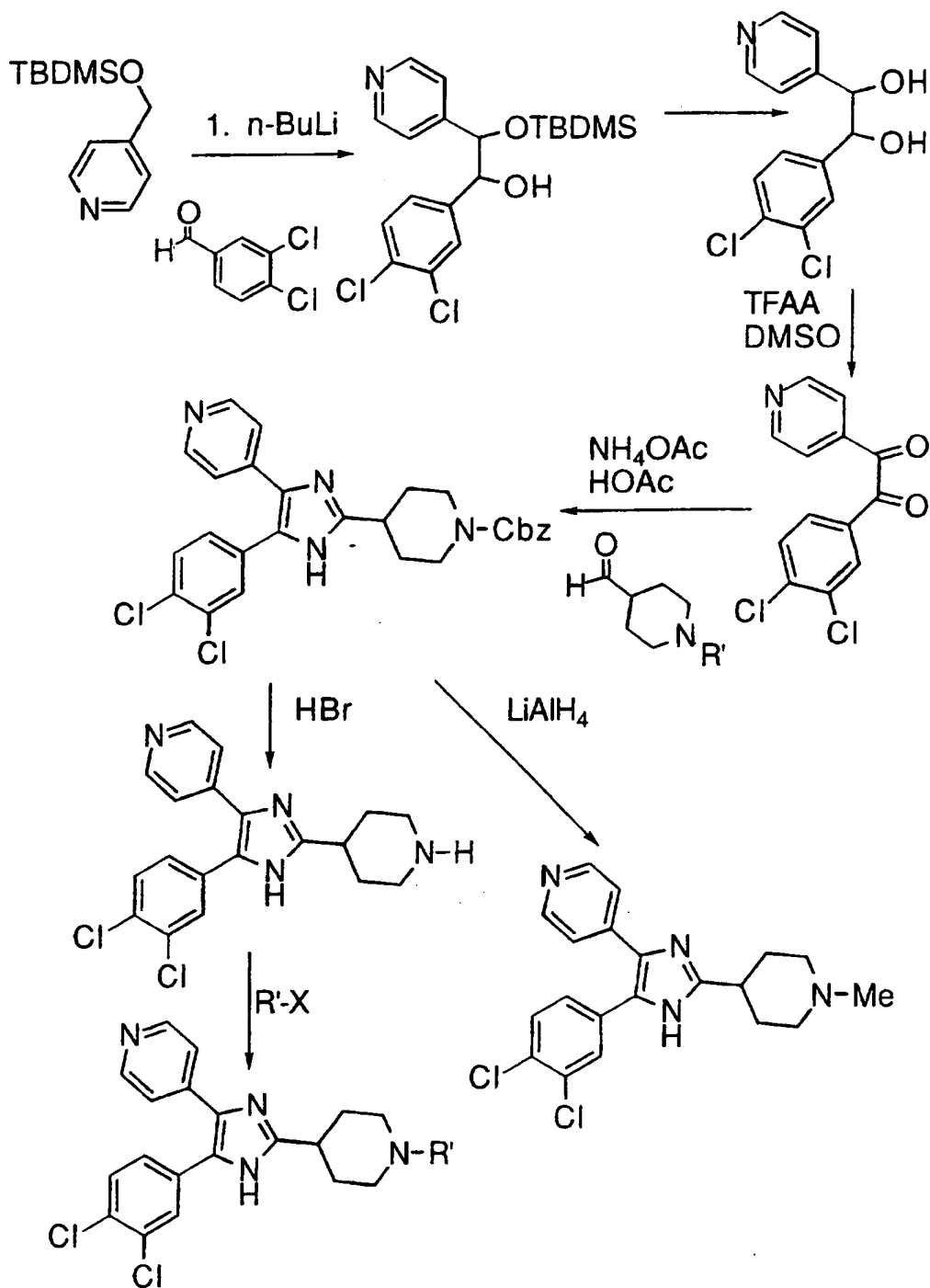
-120-

Scheme 1



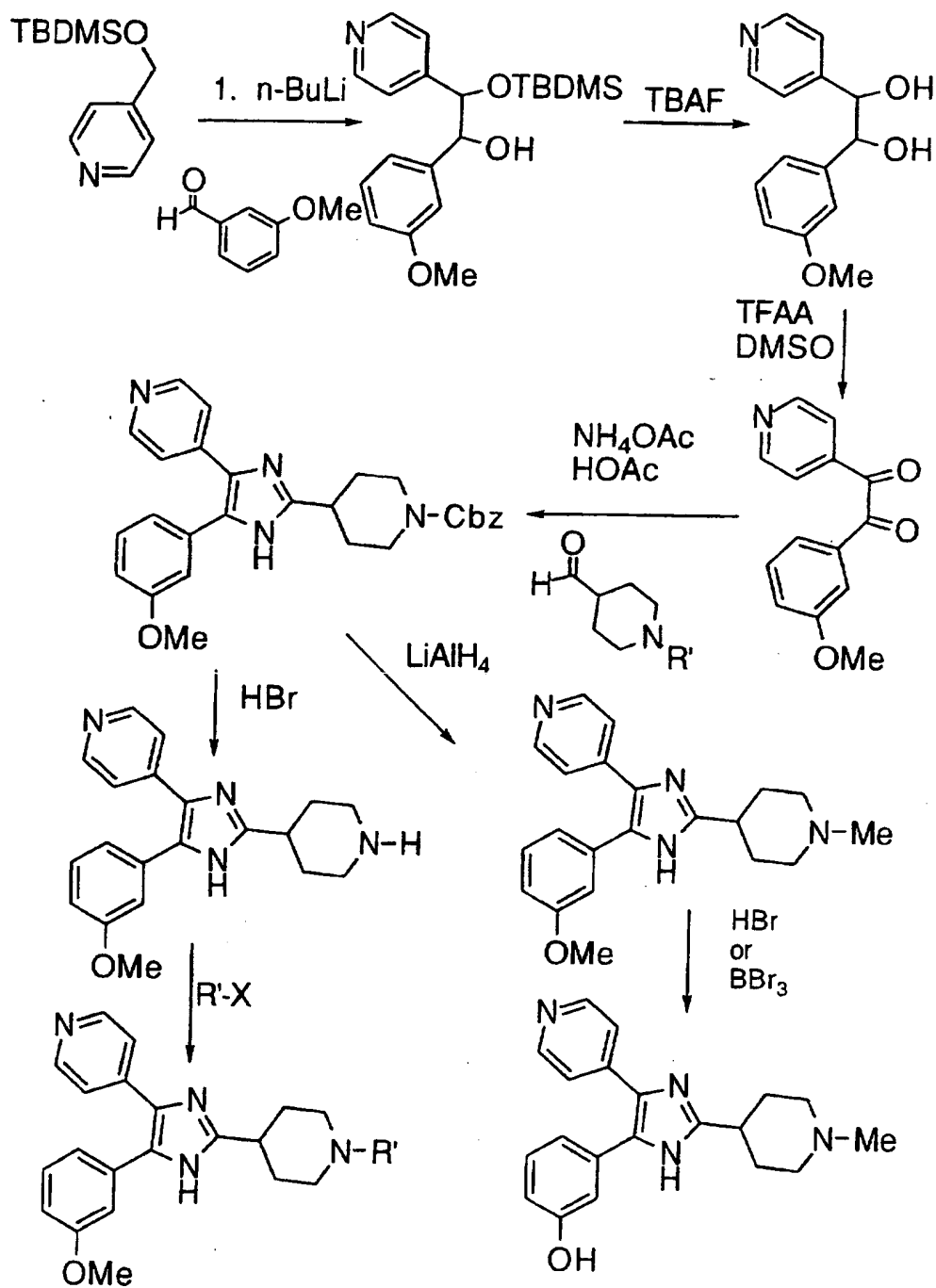
-121-

Scheme 2



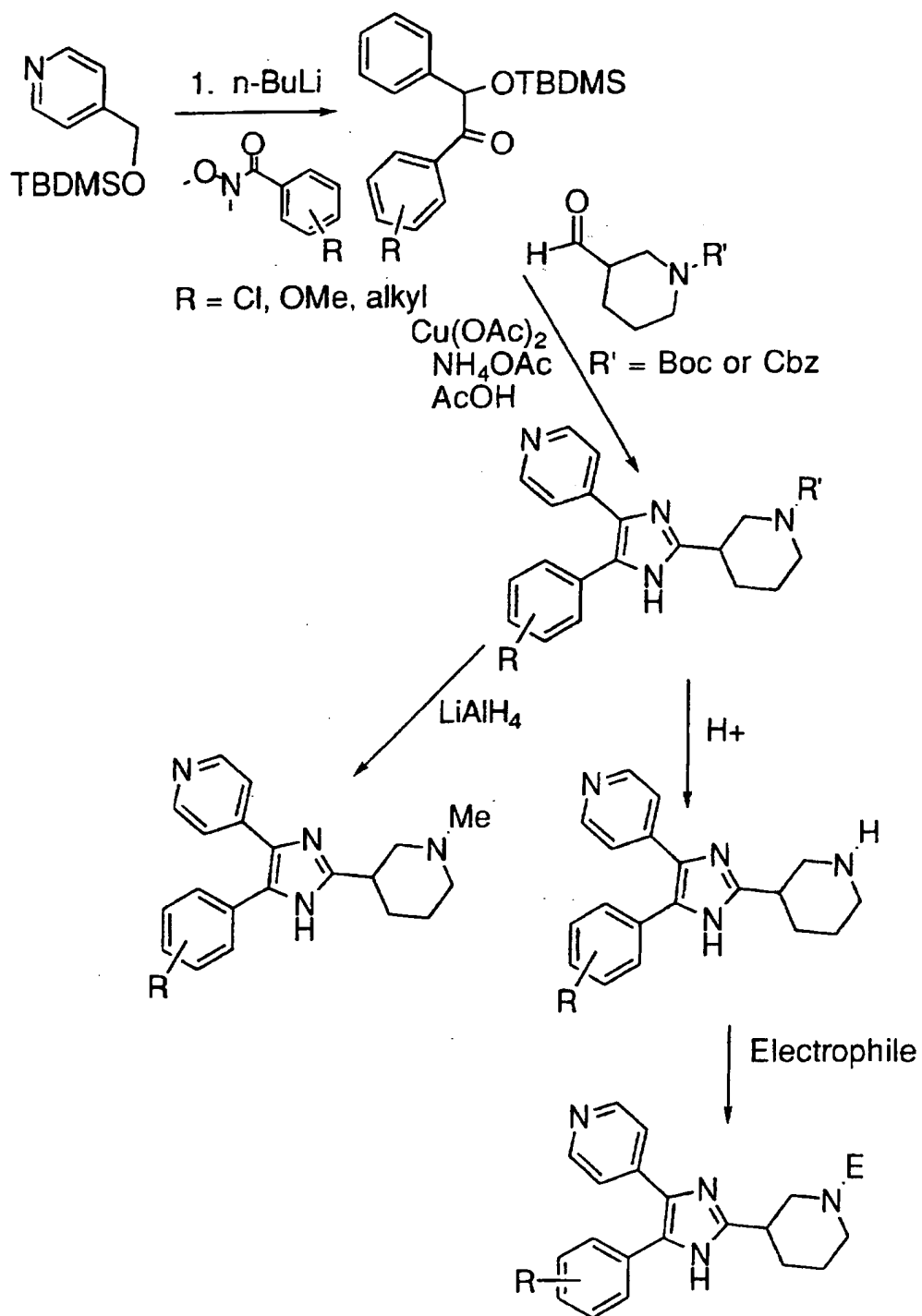
-122-

Scheme 3



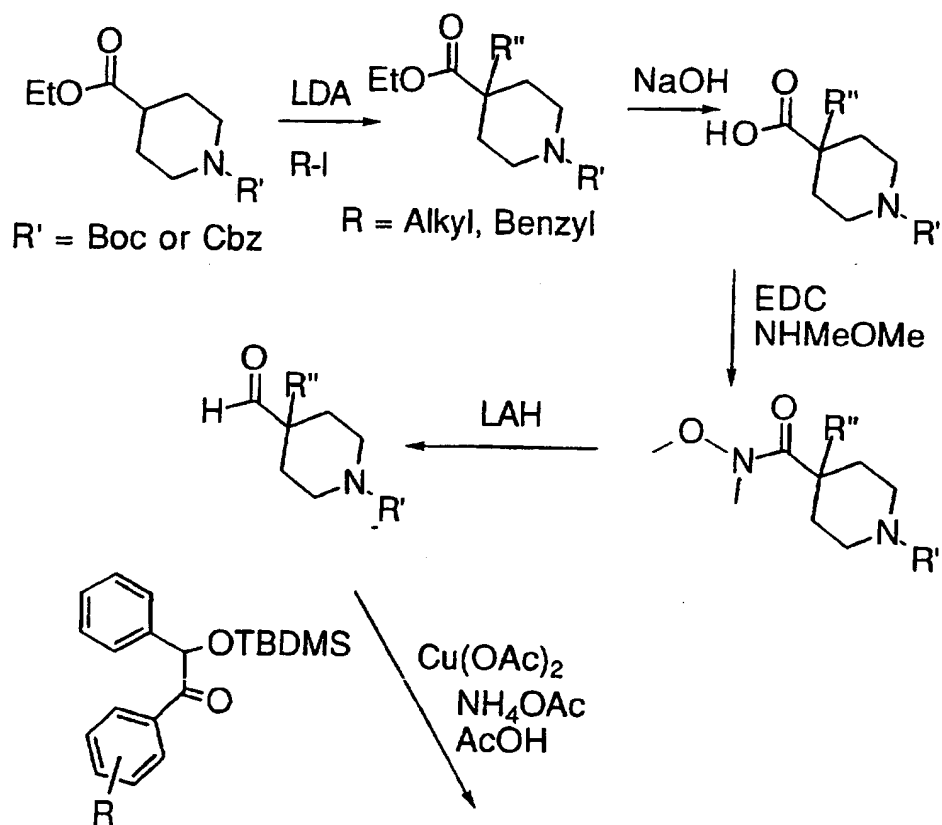
-123-

Scheme 4

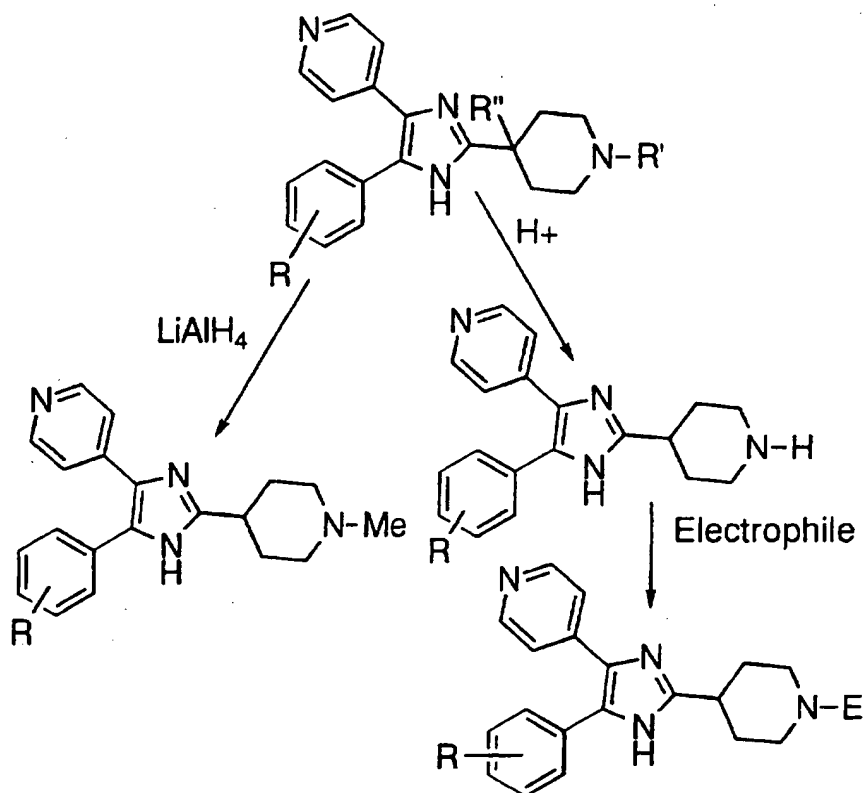


-124-

Scheme 5



-125-



TBDMSO refers to t-butyldimethylsilyloxy, TFAA refers to trifluoroacetic anhydride, TBDMS refers to t-butyldimethylsilyl,
 5 TBAF refers to tetrabutyl ammonium fluoride, Cbz refers to carboxyl-benzyl, Ac refers to acetyl, and LDA refers to lithium diisopropyl amide.

E represents an electrophile attached to the heterocyclic ring nitrogen atom. Examples of suitable electrophiles include alkyl
 10 halides, alkyl triflates, alkyl mesylates, benzyl halides, vinyl pyridine and the like. Hence, E represents alkyl, benzyl, vinyl and the like.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which
 15 provide the desired pharmacokinetic properties, palatability, absorption,

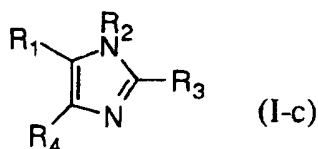
-126-

distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

Compounds of formula (I-c)



may be prepared using procedures described in PCT/US94/08297 published on 2 February 1995 and in U.S. Application No. 60/005,521 filed on October 13, 1995. Suitable procedures are also described in U.S. Patent Nos. 3,707,475 and 3,940,486.

-127-

The Raf antagonists described herein are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methane-sulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The farnesyl transferase inhibitors of formula (II-a) through (II-c) can be synthesized in accordance with reaction schemes 1-16, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^a and R^b , as shown in the Schemes, represent the substituents R^2 , R^3 , R^4 , and R^5 ; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

-128-

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Schemes.

5

Synopsis of reaction Schemes 1-16:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. In Scheme 1, for example, the synthesis of 2-alkyl substituted piperazines is outlined, and is essentially that described by J. S. Kiely and S. R. Priebe in Organic Preparations and Proceedings Int., 1990, 22, 761-768. Boc-protected amino acids I, available commercially or by procedures known to those skilled in the art, can be coupled to N-benzyl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexylcarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in a solvent such as methylene chloride, chloroform, dichloroethane, or in dimethylformamide. The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV, which is protected as the Boc derivative V. The N-benzyl group can be cleaved under standard conditions of hydrogenation, e.g., 10% palladium on carbon at 60 psi hydrogen on a Parr apparatus for 24-48 h. The product VI can be treated with an acid chloride, or a carboxylic acid under standard dehydrating conditions to furnish the carboxamides VII. A final acid deprotection step gives the intermediate VIII (Scheme 2). Intermediate VIII can be reductively alkylated with a variety of aldehydes, such as IX, prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75, from the appropriate amino acid (Scheme 3). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride

-129-

or sodium cyanoborohydride, in a solvent such as dichloroethane, methanol or dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII, which can subsequently be reductively alkylated with a second aldehyde to obtain XIII. Removal of the protecting group, and conversion to the cyclized product such as the dihydroimidazole XV, can be accomplished by literature procedures.

Alternatively, the protected piperazine intermediate VII can be reductively alkylated with other aldehydes such as 1-trityl-4-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as XVI (Scheme IV) (Tr = trityl). The trityl protecting group can be removed from XVI to give XVII, or alternatively, XVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XVIII. Alternatively, the intermediate VIII can be acylated or sulfonylated by standard techniques. The imidazole acetic acid XIX can be converted to the acetate XXI by standard procedures, and XXI can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XXII. Hydrolysis and reaction with piperazine VIII in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXIV.

If the piperazine VIII is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXV in Scheme 6, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 6, 7). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIX. In addition, the fully deprotected amino alcohol XXX can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXXI (Scheme 7), or tertiary amines.

-130-

The protected amino alcohol XXVII can also be utilized to synthesize 2-aziridinylmethylpiperazines such as XXXII (Scheme 8).

Treating XXVII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide leads to the formation of aziridine XXXII. The aziridine reacts in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXXIII.

Piperazine VIII can be reacted with an aldehyde derived from an amino acid, such as an O-alkylated tyrosine, to obtain compounds such as XXXIX. When R' is an aryl group, XXXIX can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XL. Alternatively, the amine protecting group in XXXIX can be removed, and O-alkylated phenolic amines such as XLI produced.

Depending on the identity of the amino acid I, various side chains can be incorporated onto the piperazine. For example, when I is a protected β -benzyl ester of aspartic acid, the intermediate diketopiperazine XLII (where $n=1$ and $R=\text{benzyl}$) is obtained, as shown in Scheme 10. Subsequent reduction reduces the ester to the alcohol XLIII, which can then be reacted with a variety of alkylating agents such as an alkyl iodide, under basic conditions, for example, sodium hydride in dimethylformamide or tetrahydrofuran. The resulting ether XLIV can then be carried on to final products as described in Schemes 3-9.

N-Aryl piperazines can be prepared as described in Scheme 11. An aryl amine XLV is reacted with *bis*-chloroethyl amine hydrochloride (XLVI) in refluxing *n*-butanol to furnish compounds XLVII. The resulting piperazines XLVII can then be carried on to final products as described in Schemes 3-9.

Piperazin-5-ones can be prepared as shown in Scheme 12. Reductive amination of protected amino aldehydes XLIX (prepared from I as described previously) gives rise to compound L. This is then reacted with bromoacetyl bromide under Schotten-Baumann conditions. Ring closure is effected with a base, such as sodium hydride, in a polar

-131-

aprotic solvent, such as dimethylformamide, to give LI. The carbamate protecting group is removed under acidic conditions, such as trifluoroacetic acid in methylene chloride or hydrogen chloride gas in methanol or ethyl acetate, and the resulting piperazine can then be carried on to
5 final products as described in Schemes 3-9.

The isomeric piperazin-3-ones can be prepared as described in Scheme 13. The imine formed from arylcarboxamides LII and 2-aminoglycinal diethyl acetal (LIII) can be reduced under a variety of conditions, including sodium triacetoxyborohydride in dichloroethane,
10 to give the amine LIV. Amino acids I can be coupled to amines LIV under standard conditions, and the resulting amide LV when treated with aqueous acid in tetrahydrofuran can cyclize to the unsaturated LVI. Catalytic hydrogenation under standard conditions gives the requisite intermediate LVII, which is elaborated to final products as
15 described in Schemes 3-9.

Access to alternatively substituted piperazines is described in Scheme 14. Following deprotection, e.g., with trifluoroacetic acid, the N-benzyl piperazine V can be acylated with an aryl carboxylic acid. The resulting N-benzyl aryl carboxamide LIX can be hydrogenated in
20 the presence of a catalyst to give the piperazine carboxamide LX which can then be carried on to final products as described in Schemes 3-9.

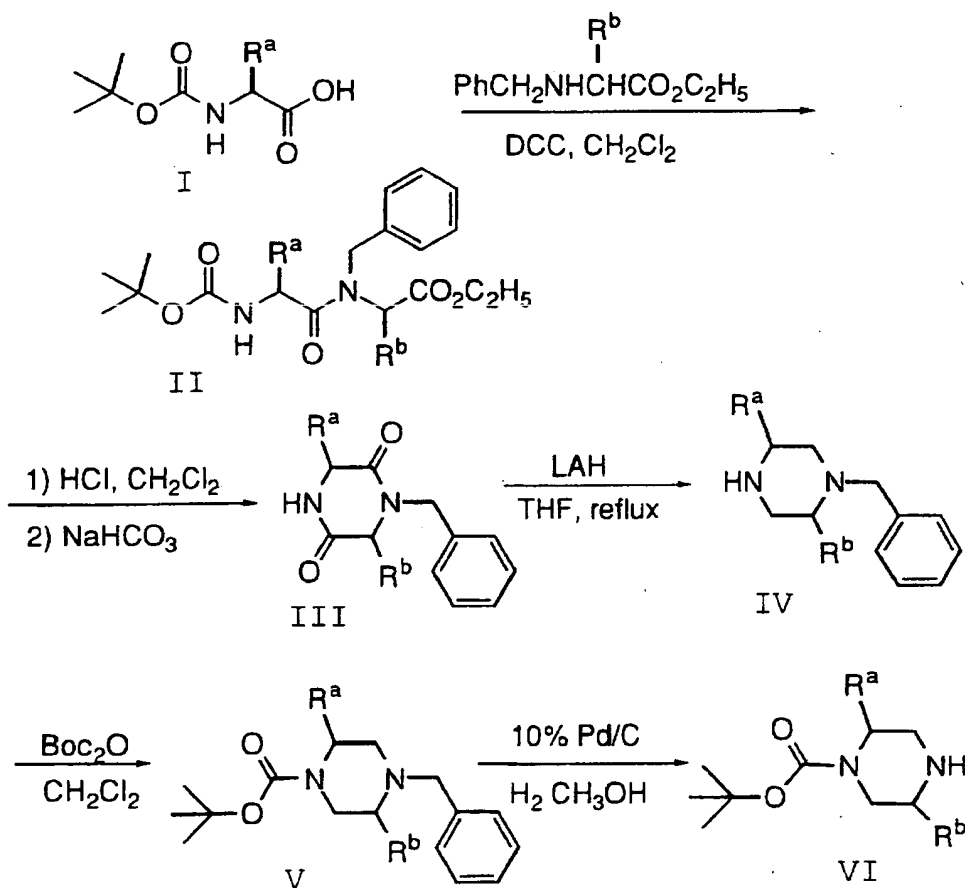
Reaction Scheme 15 provides an example of the synthesis of compounds wherein the substituents R^2 and R^3 are combined to form $-(CH_2)_u-$. For example, 1-aminocyclohexane-1-carboxylic acid
25 LXI can be converted to the spiropiperazine LXVI essentially according to the procedures outlined in Schemes 1 and 2. The piperazine intermediate LXIX can be deprotected as before, and carried on to final products as described in Schemes 3-9. It is understood that reagents utilized to provide the substituent Y which is 2-(naphthyl) and the
30 imidazolylalkyl substituent may be readily replaced by other reagents well known in the art and readily available to provide other N-substituents on the piperazine.

The aldehyde XLIX from Scheme 12 can also be reductively alkylated with an aniline as shown in Scheme 16. The

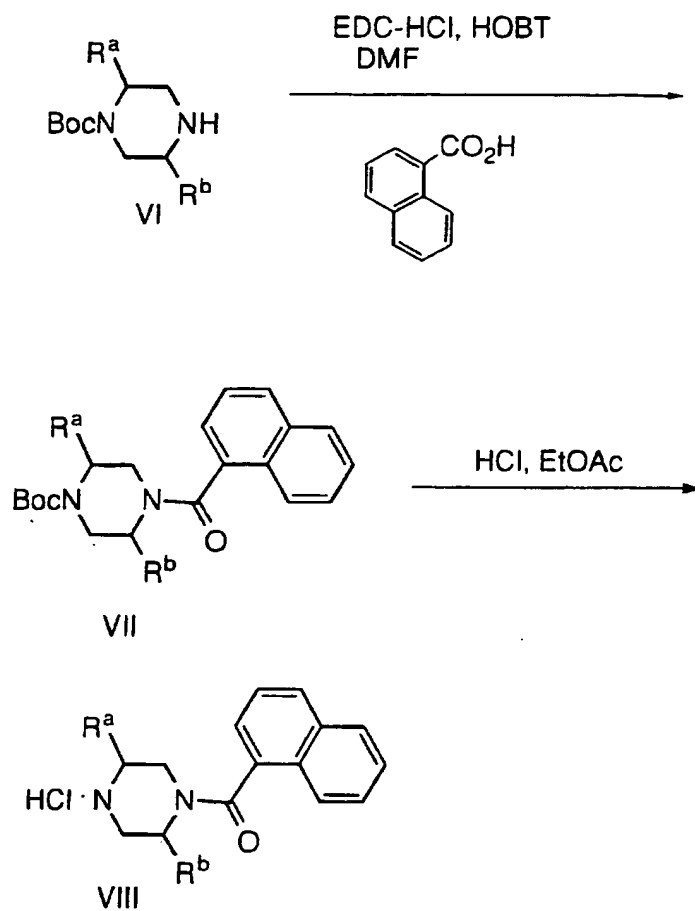
-132-

- product LXXI can be converted to a piperazinone by acylation with chloroacetyl chloride to give LXXII, followed by base-induced cyclization to LXXIII. Deprotection, followed by reductive alkylation with a protected imidazole carboxaldehyde leads to LXXV, which can be alkylated with an arylmethylhalide to give the imidazolium salt LXXVI. Final removal of protecting groups by either solvolysis with a lower alkyl alcohol, such as methanol, or treatment with triethylsilane in methylene chloride in the presence of trifluoroacetic acid gives the final product LXXVII.
- 5

SCHEME 1

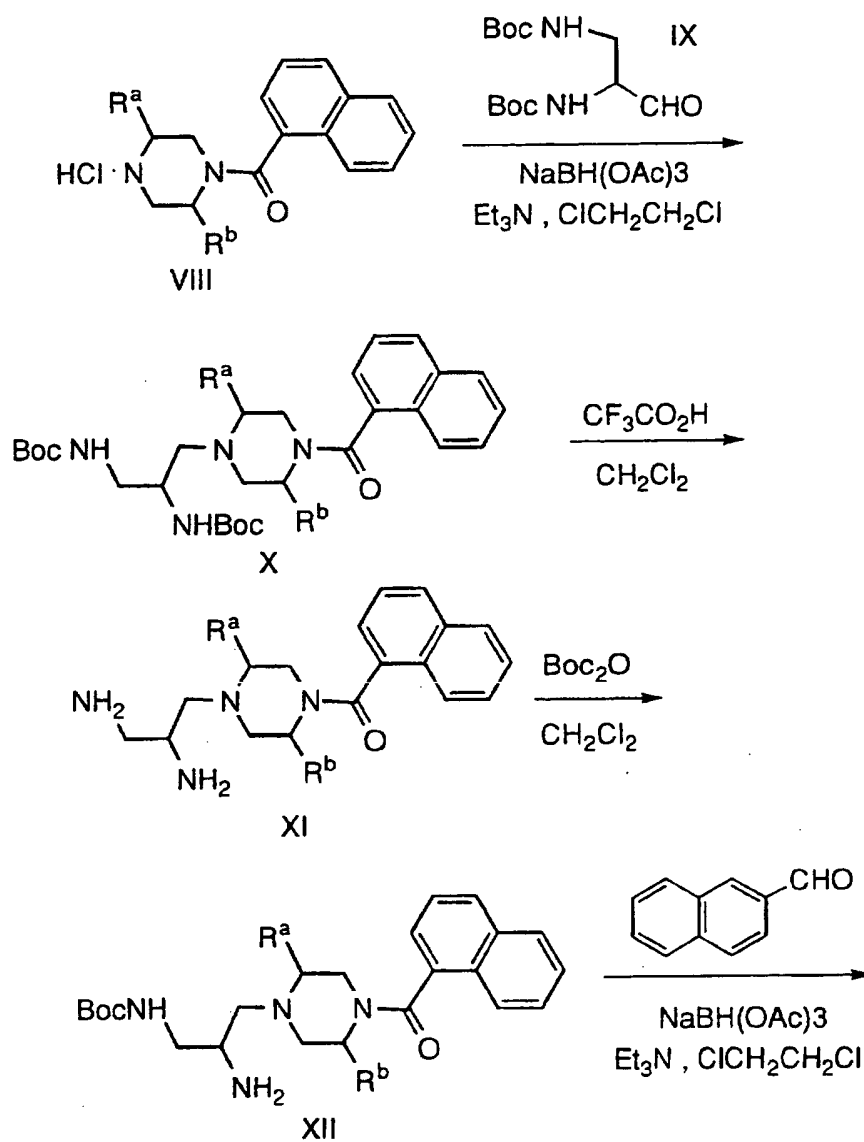


-133-

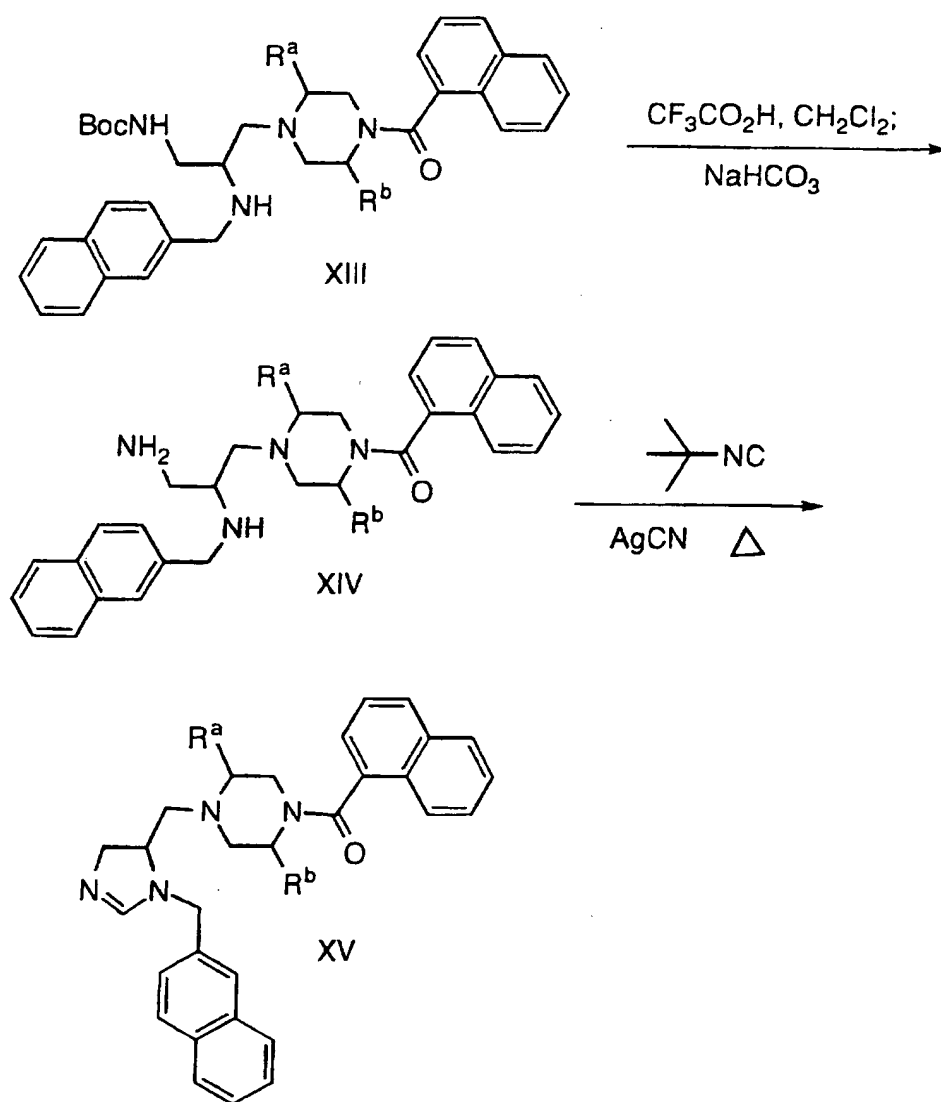
SCHEME 2

-134-

SCHEME 3

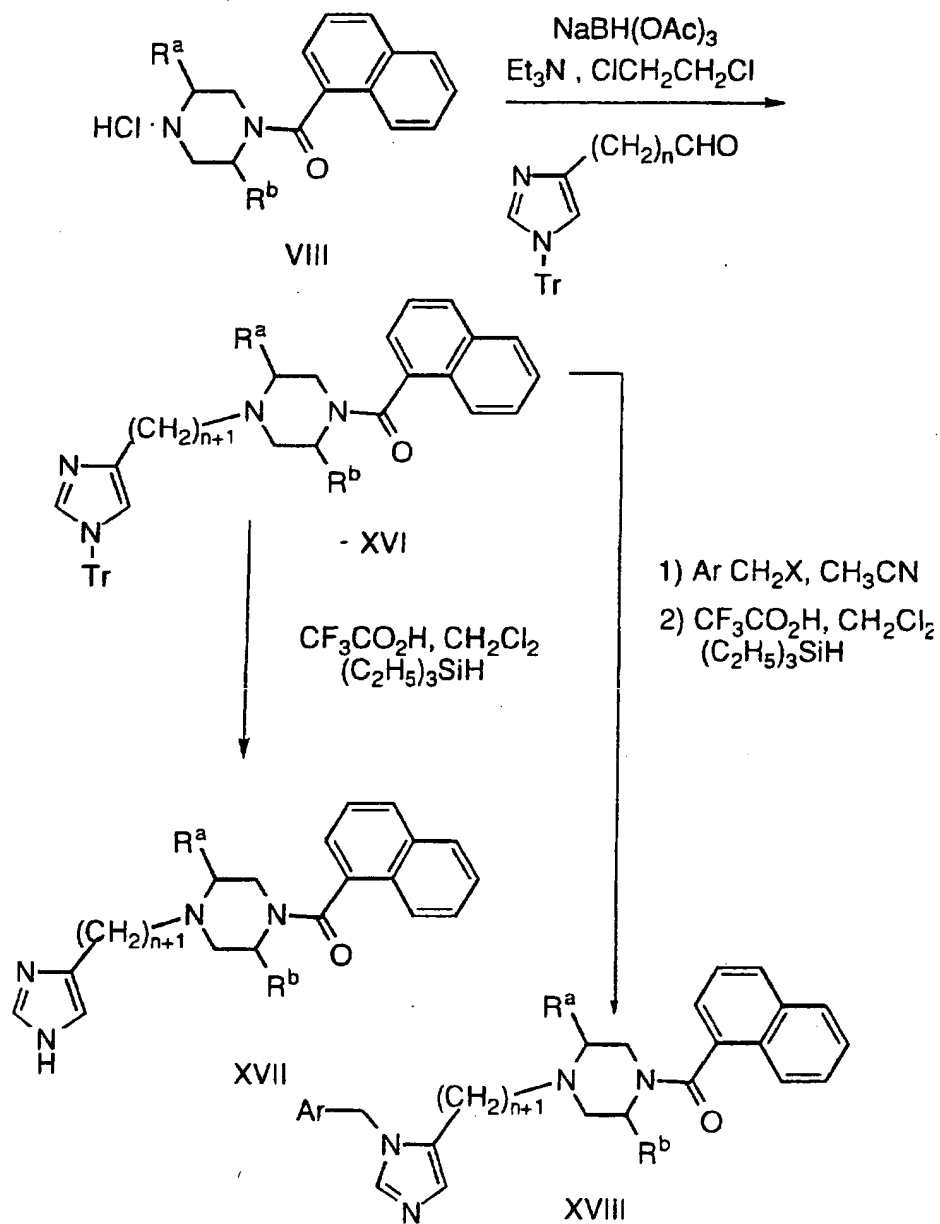


-135-

SCHEME 3 (Cont.)

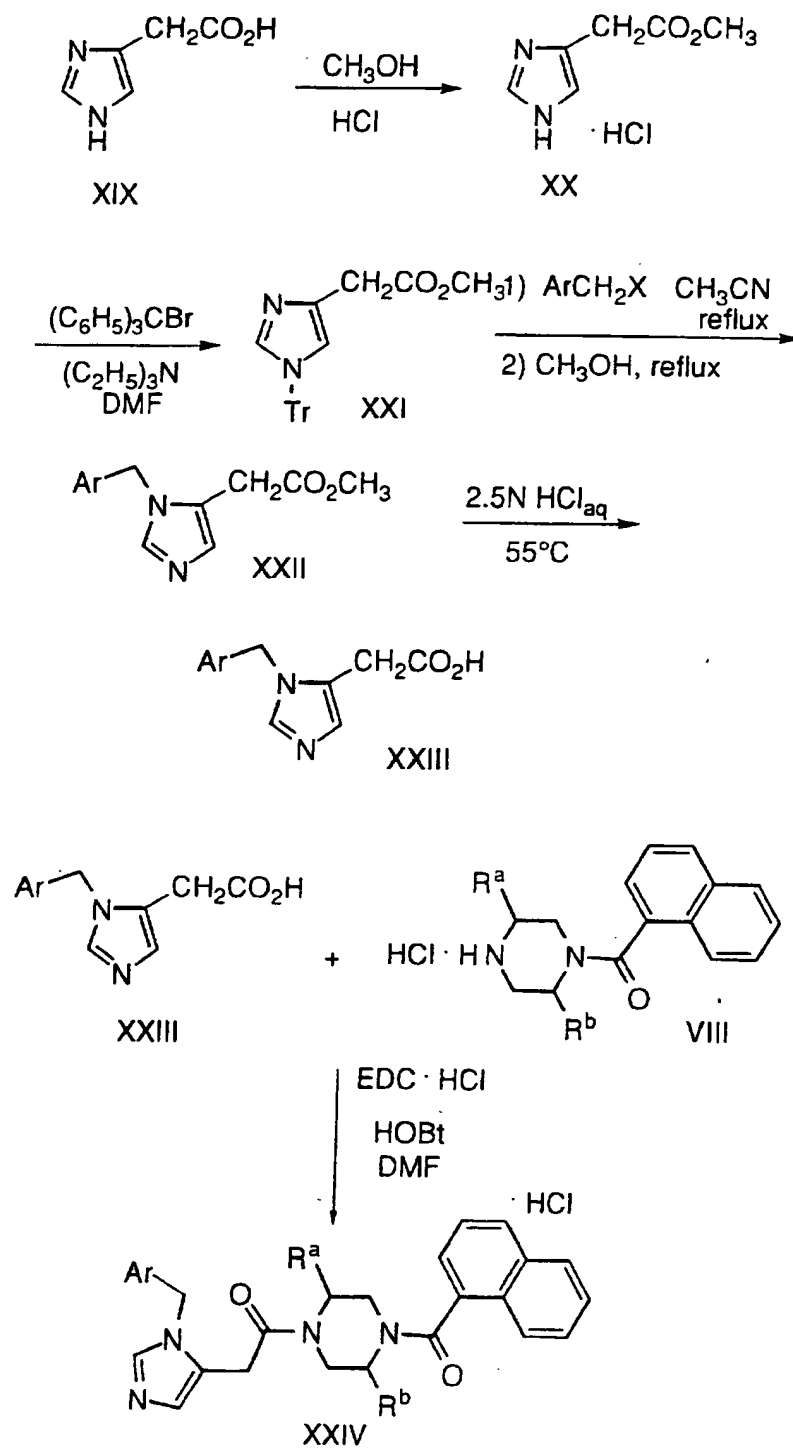
-136-

SCHEME 4

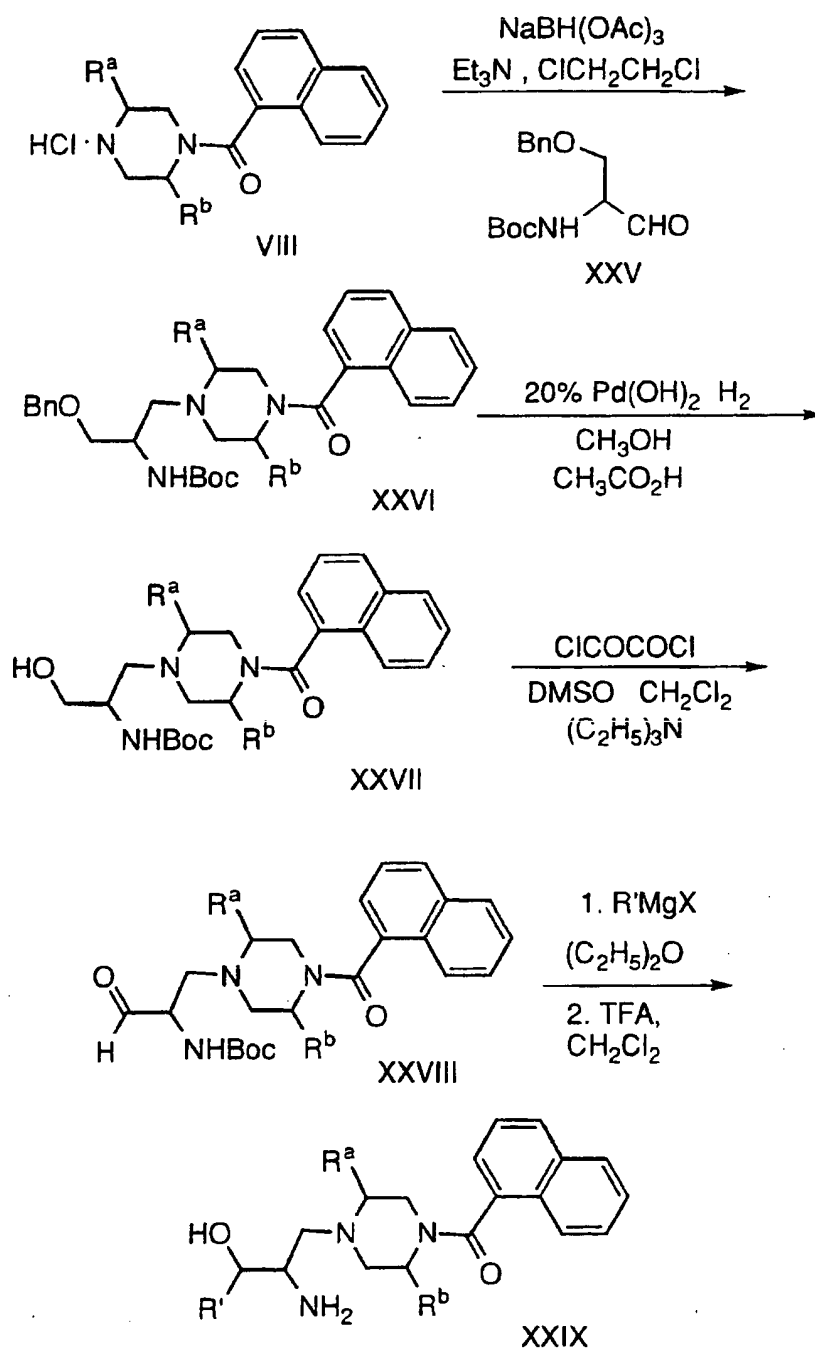


-137-

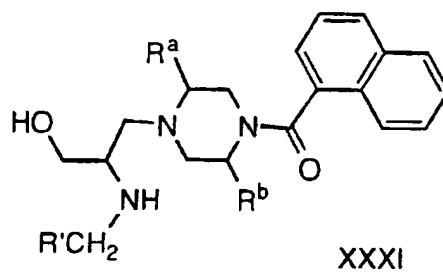
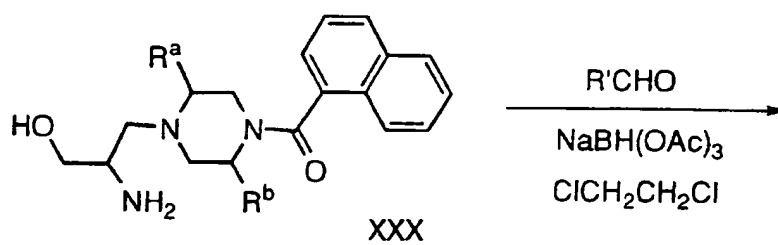
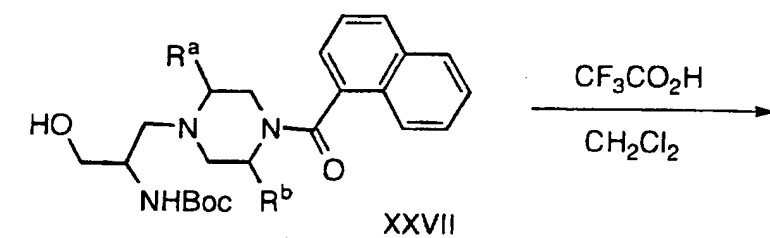
SCHEME 5



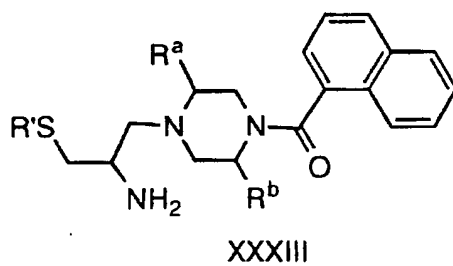
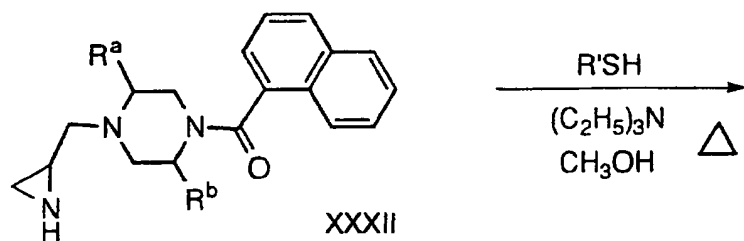
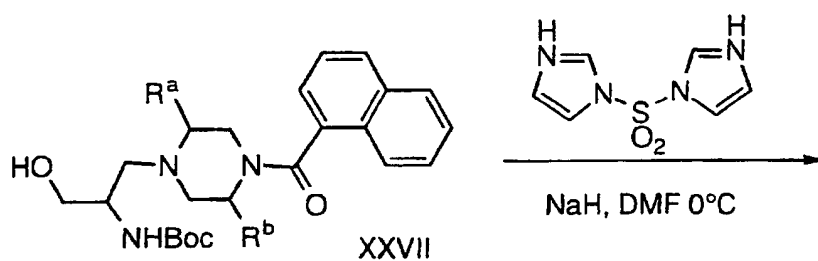
-138-

SCHEME 6

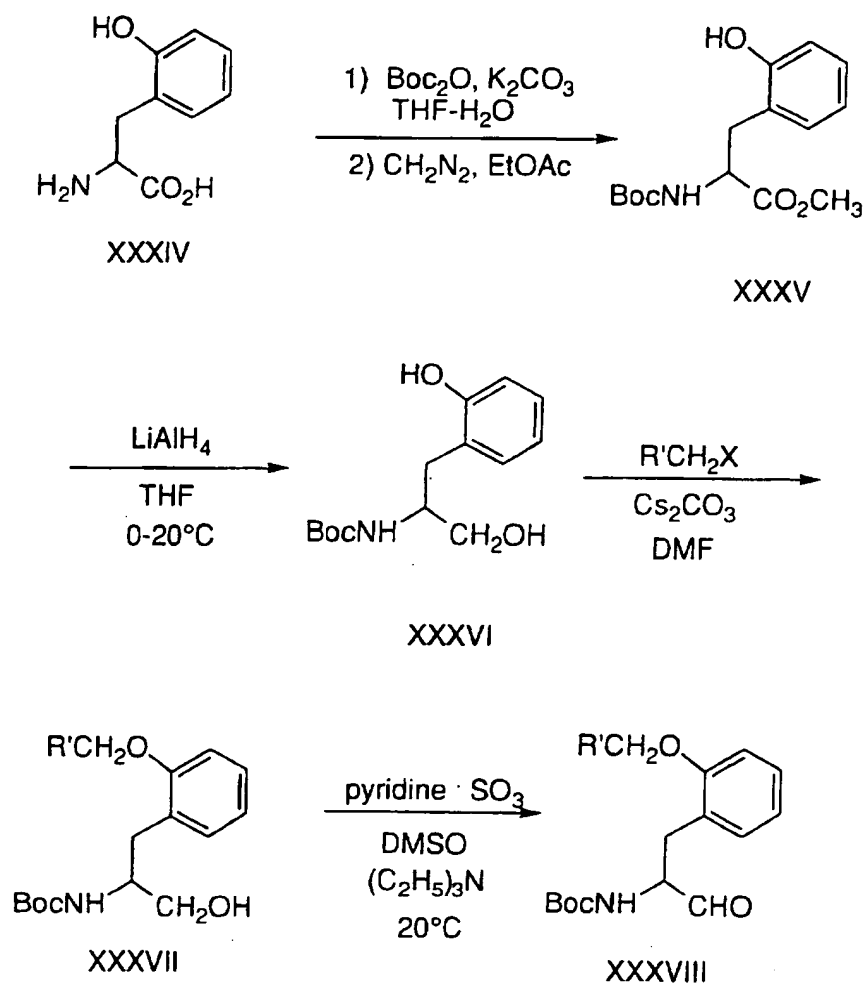
-139-

SCHEME 7

-140-

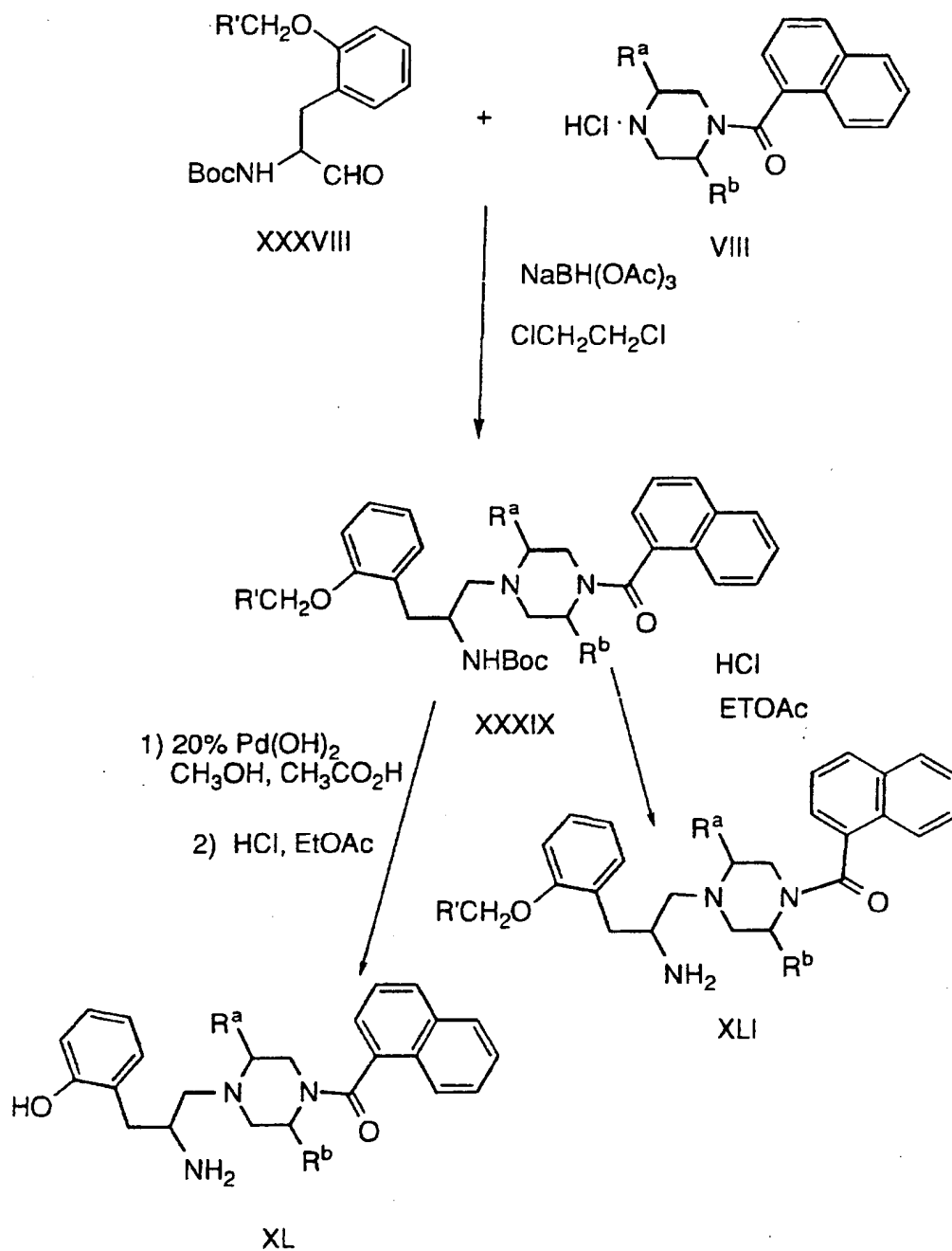
SCHEME 8

-141-

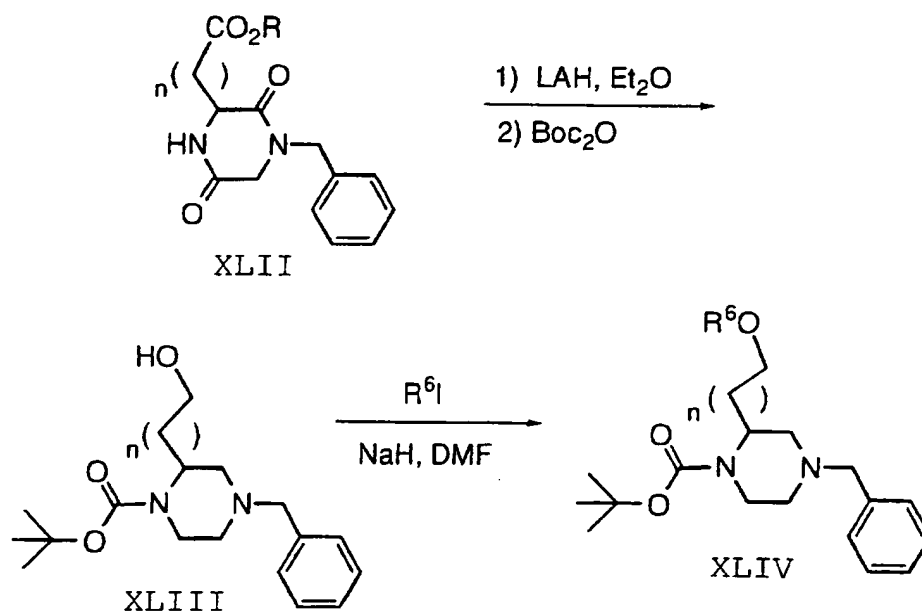
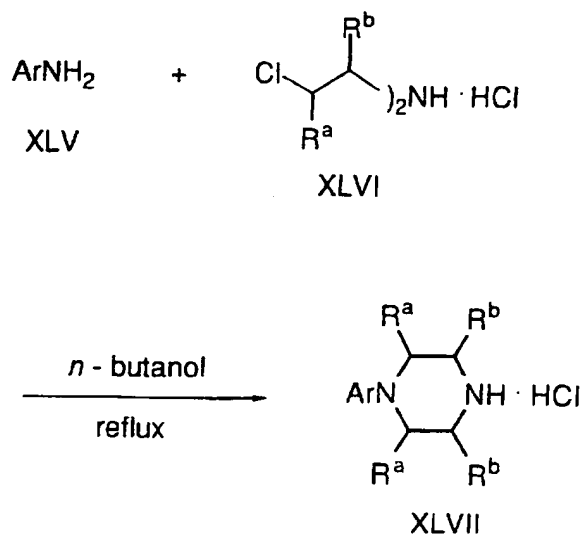
SCHEME 9

-142-

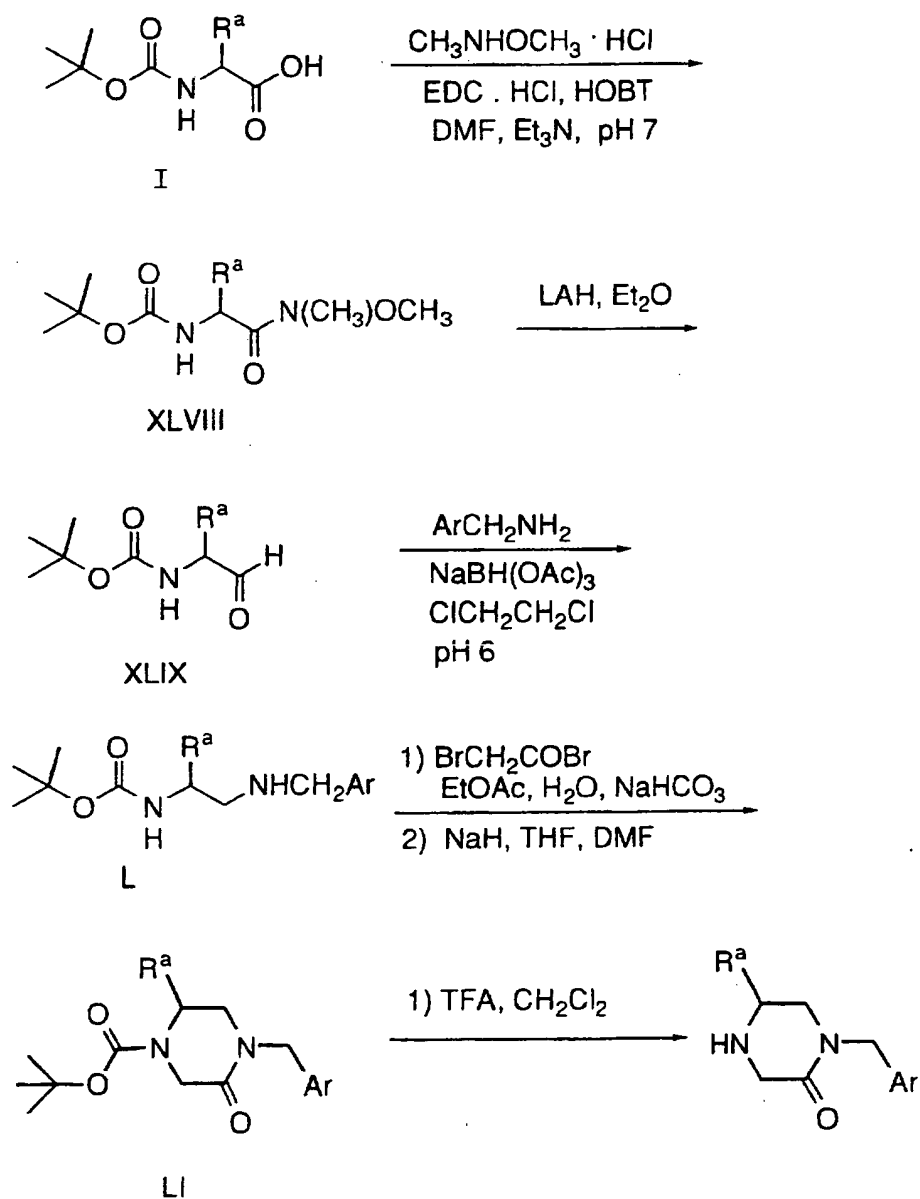
SCHEME 9 (continued)



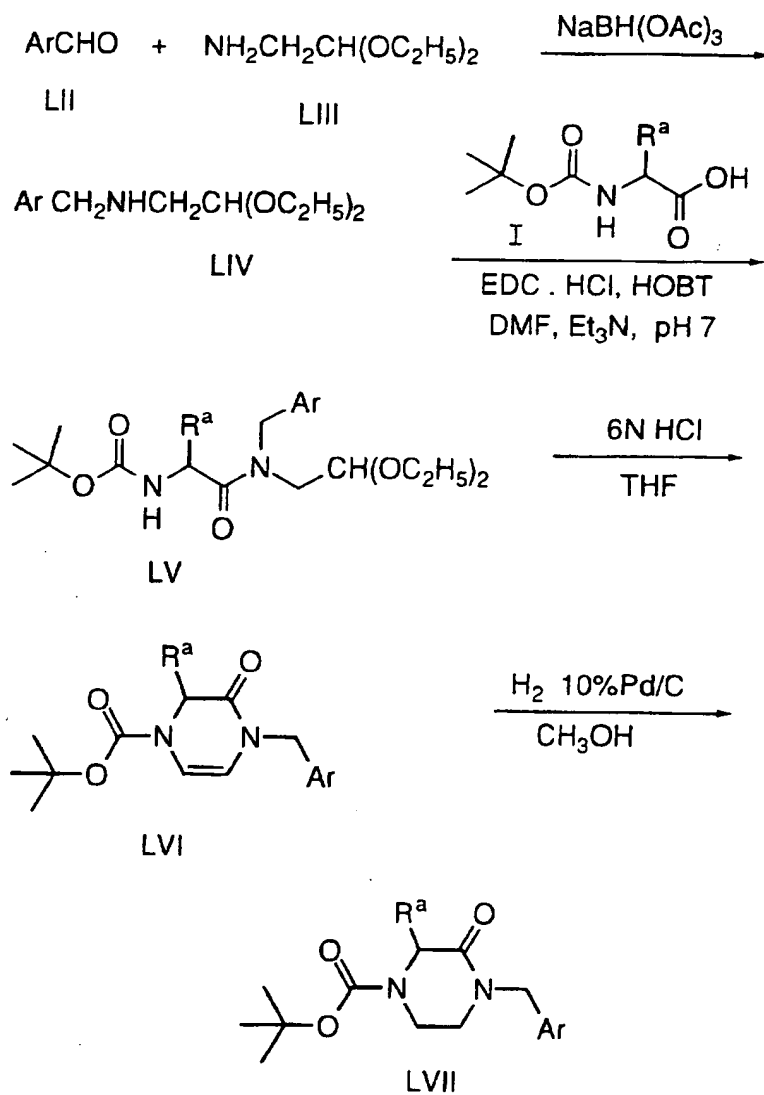
-143-

SCHEME 10SCHEME 11

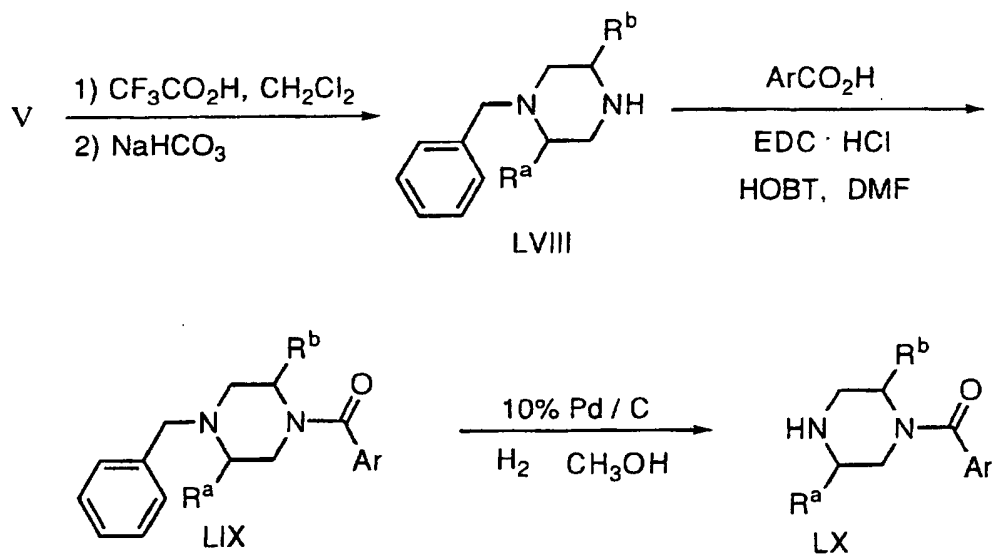
-144-

SCHEME 12

-145-

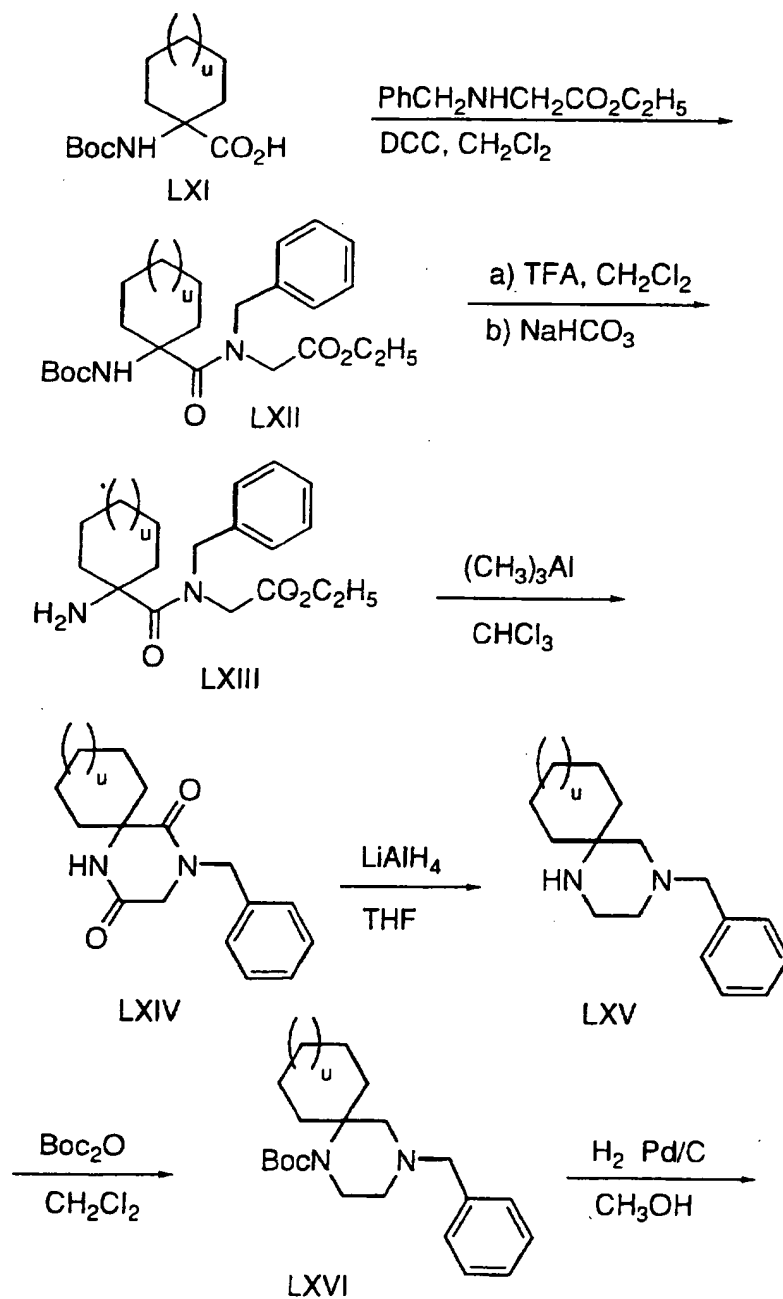
SCHEME 13

-146-

SCHEME 14

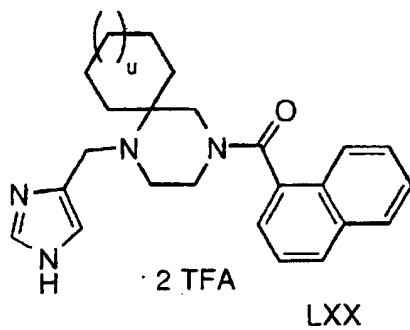
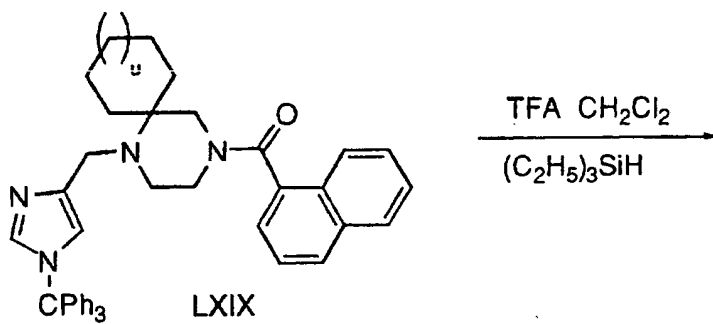
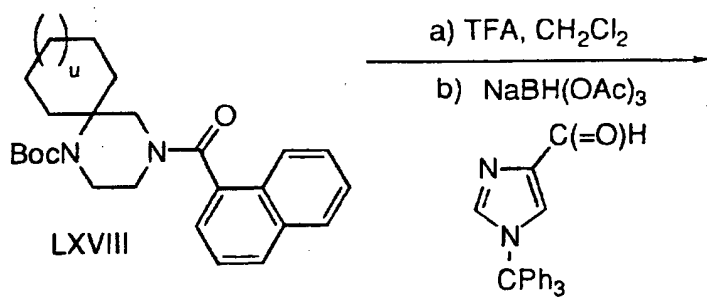
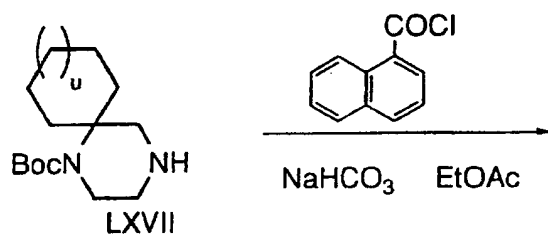
-147-

SCHEME 15

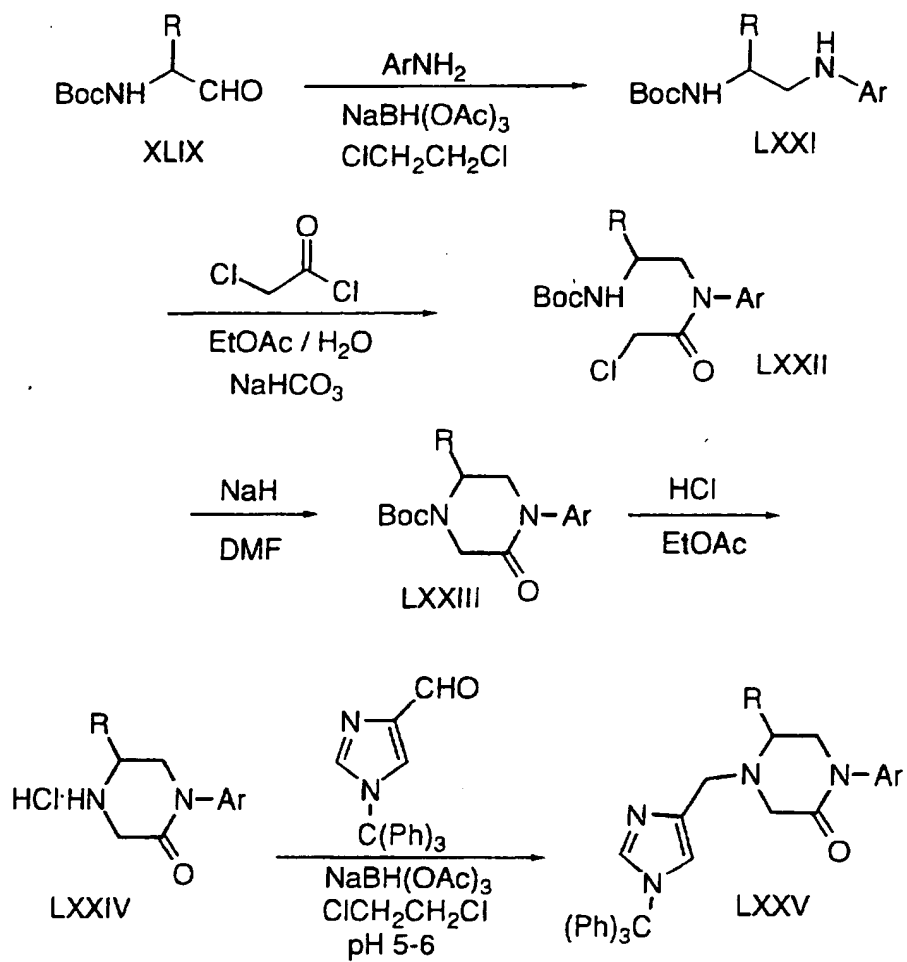


-148-

SCHEME 15 (continued)

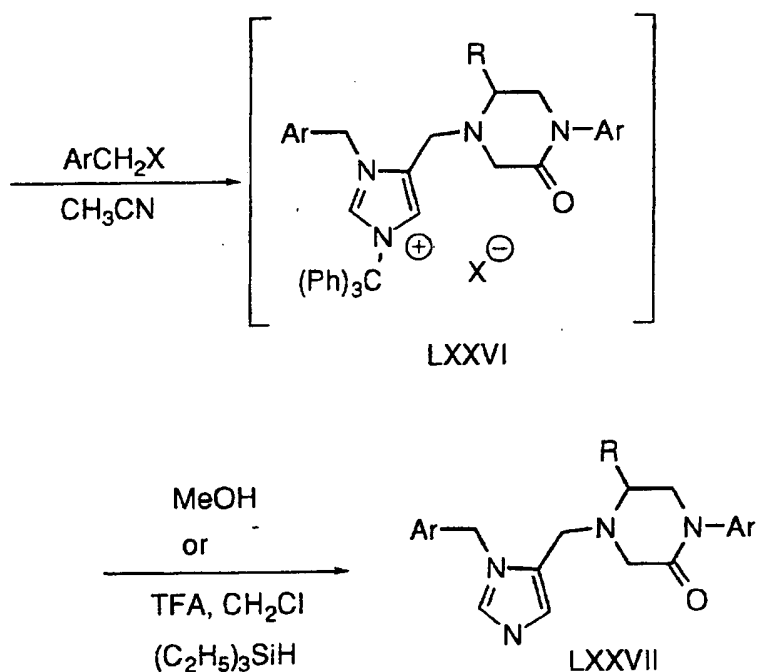


-149-

SCHEME 16

-150-

Scheme 6 (Continued)



5

The farnesyl transferase inhibitors can be synthesized in accordance with the general reaction schemes in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Some key bond-forming and peptide modifying reactions are:

15 **Reaction A** Amide bond formation and protecting group cleavage using standard solution or solid phase methodologies.

Reaction B Preparation of a reduced peptide subunit by reductive alkylation of an amine by an aldehyde using sodium cyanoborohydride or other reducing agents.

20

-151-

Reaction C Alkylation of a reduced peptide subunit with an alkyl or aralkyl halide or, alternatively, reductive alkylation of a reduced peptide subunit with an aldehyde using sodium cyanoborohydride or other reducing agents.

5

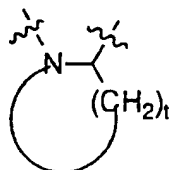
Reaction D Peptide bond formation and protecting group cleavage using standard solution or solid phase methodologies.

Reaction E Preparation of a reduced subunit by borane reduction of the amide moiety.

10

Reaction Schemes A-E illustrate bond-forming and peptide modifying reactions incorporating acyclic peptide units. Such reactions are equally useful when the - NHC(R^A) - moiety of the reagents and compounds illustrated is replaced with the following moiety:

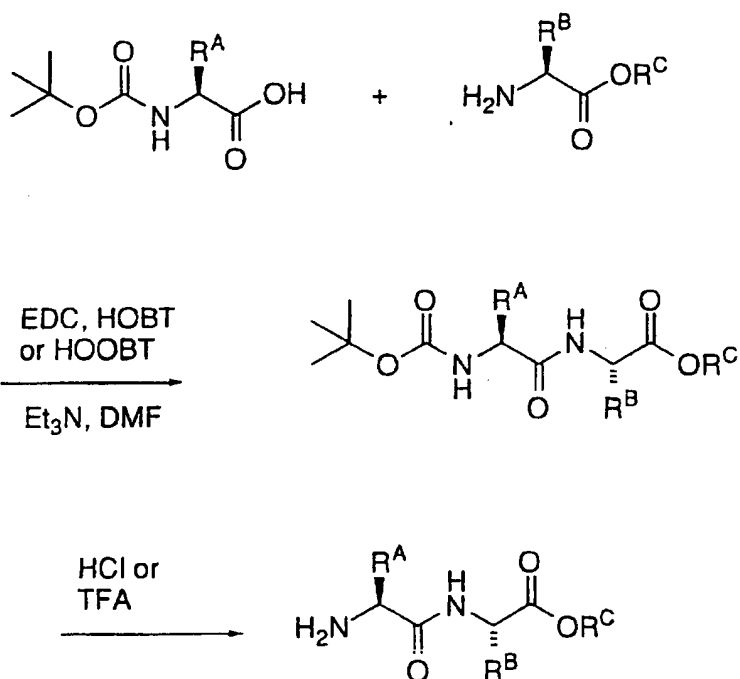
15



which can be substituted with R^{4a}, R^{4b}, R^{7a} and R^{7b} in accordance with structures (II-d) through (II-o). These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Schemes.

20

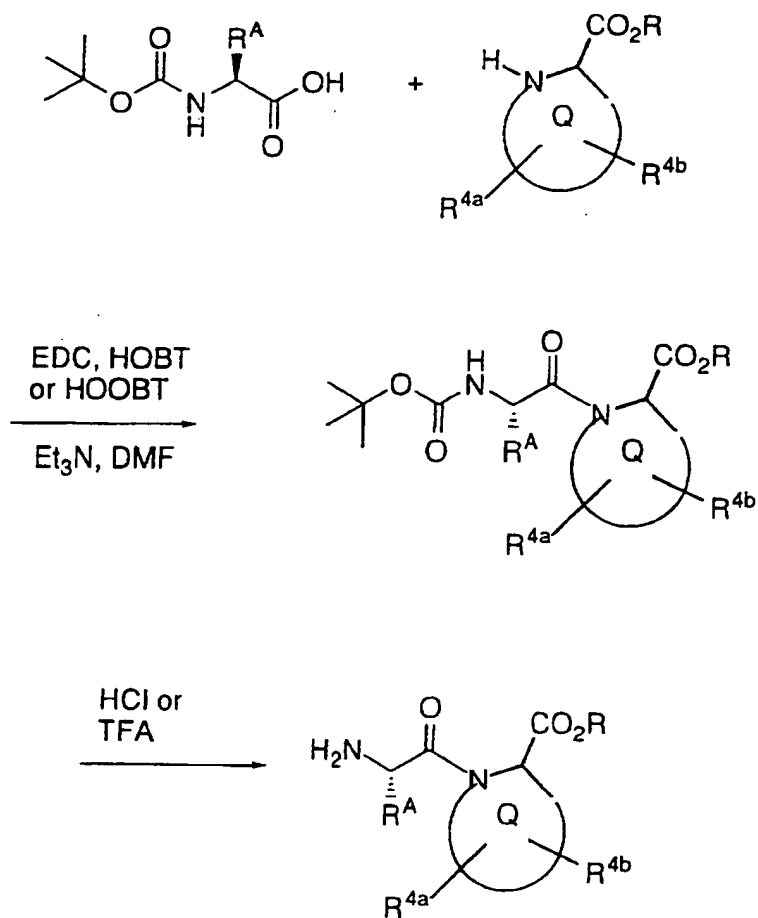
-152-

REACTION SCHEME AReaction A. Coupling of residues to form an amide bond

-153-

ALTERNATIVE REACTION SCHEME A FOR
COMPOUNDS (II-h) THROUGH (II-o)

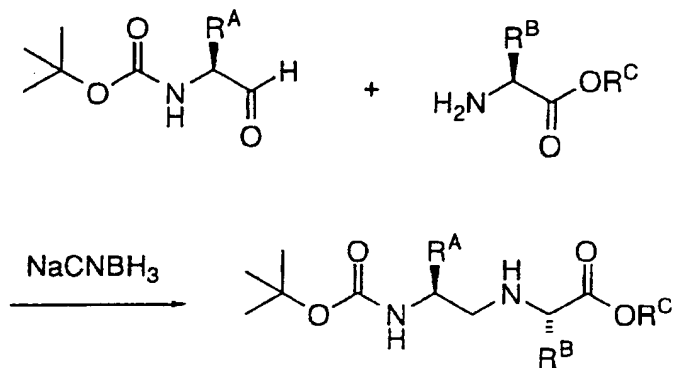
Coupling of residues to form an amide bond



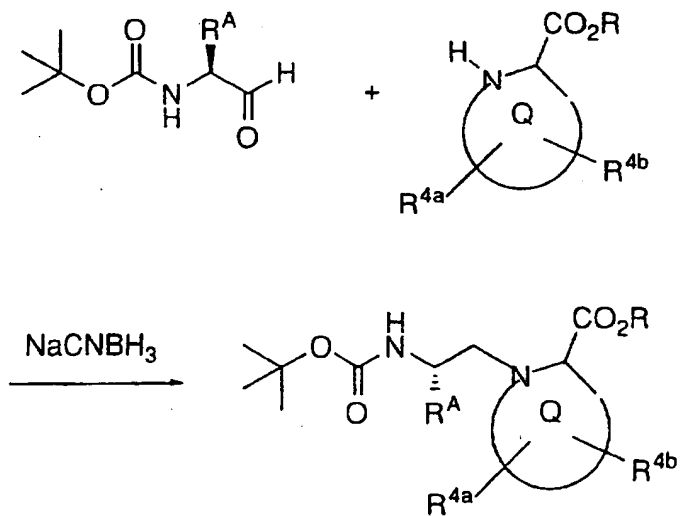
-154-

REACTION SCHEME B

Preparation of reduced peptide subunits by reductive alkylation

ALTERNATIVE REACTION SCHEME B FOR COMPOUNDS(II-h) THROUGH (II-o)

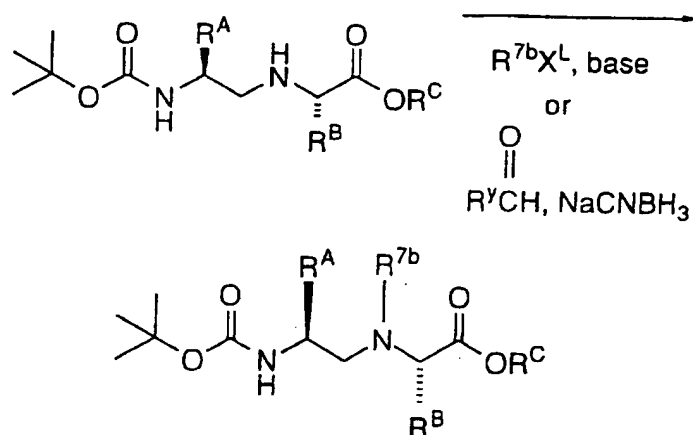
Preparation of reduced peptide subunits by reductive alkylation



-155-

REACTION SCHEME C

Alkylation/reductive alkylation of reduced peptide subunits

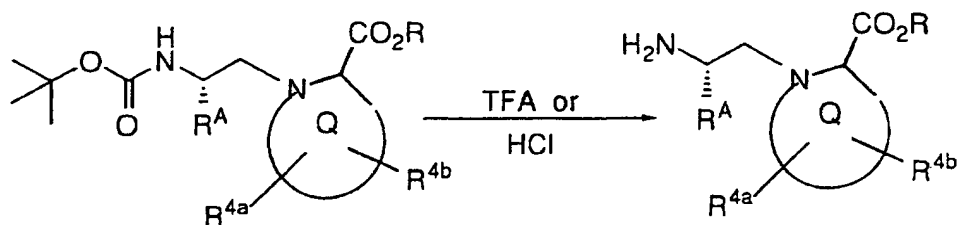


where R^A and R^B are R^3 , R^4 , R^{5a} or R^{5b} as previously defined; R^C is R^6 as previously defined or a carboxylic acid protecting group; X^L is a leaving group, e.g., Br^- , I^- or MsO^- ; and R^Y is defined such that R^{7b} is generated by the reductive alkylation process.

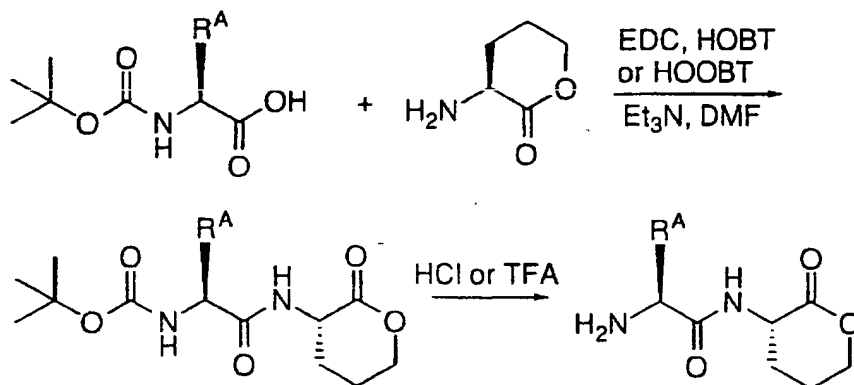
-156-

ALTERNATIVE REACTION SCHEME C for COMPOUNDS(II-h) THROUGH (II-o)

Deprotection of reduced peptide subunits

REACTION SCHEME D

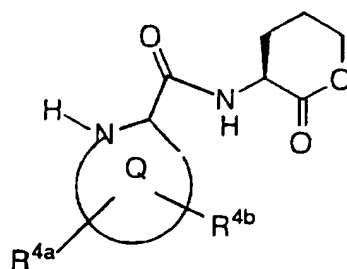
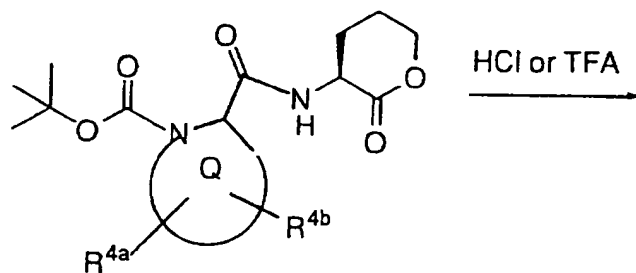
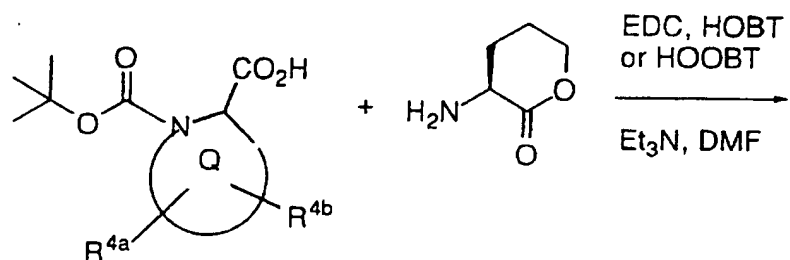
Coupling of residues to form an amide bond



-157-

ALTERNATIVE REACTION SCHEME D FOR COMPOUNDS(II-h) THROUGH (II-o)

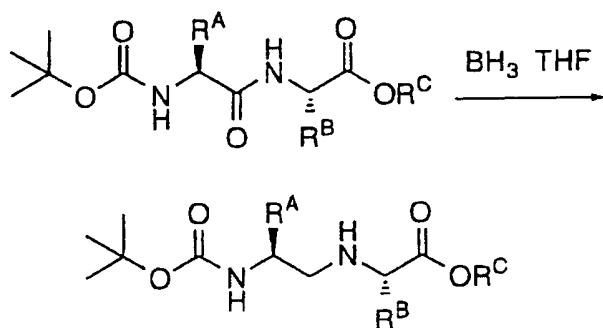
Coupling of residues to form an amide bond



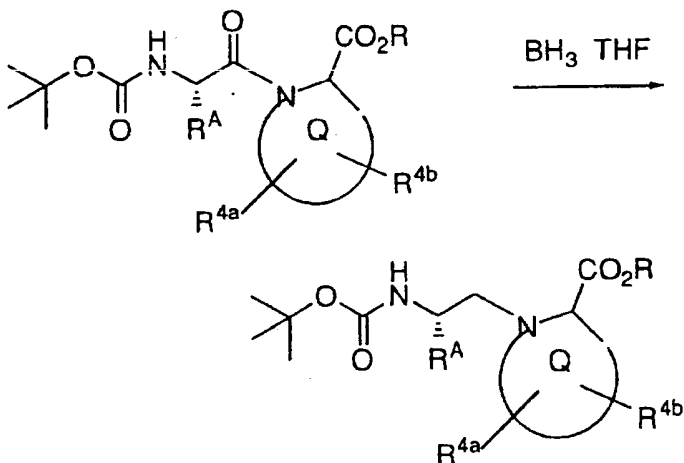
-158-

REACTION SCHEME E

Preparation of reduced dipeptides from peptides

ALTERNATIVE REACTION SCHEME E FOR COMPOUNDS(II-h) THROUGH (II-o)

Preparation of reduced dipeptides from peptides



All variables are as defined above.

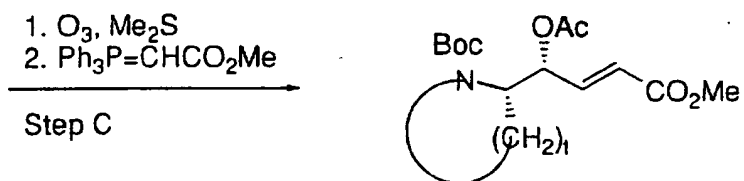
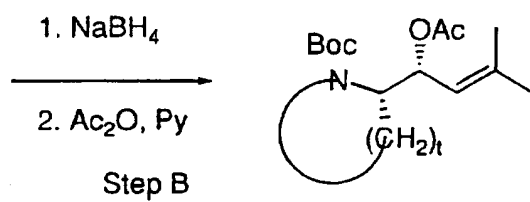
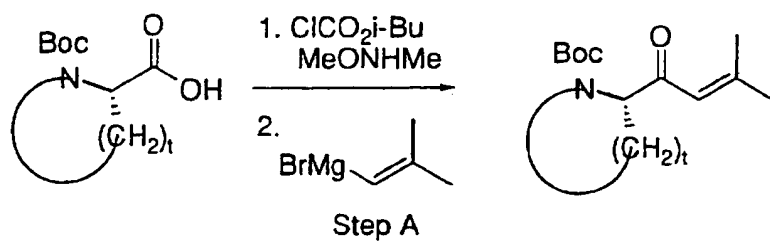
- 5 Certain compounds wherein X-Y is an ethenylene or ethylene unit are prepared by employing the reaction sequences shown in Reaction Schemes F and G. Scheme F outlines the preparation of the alkene isosteres utilizing standard manipulations such as Weinreb amide formation, Grignard reaction, acetylation, ozonolysis, Wittig reaction,

-159-

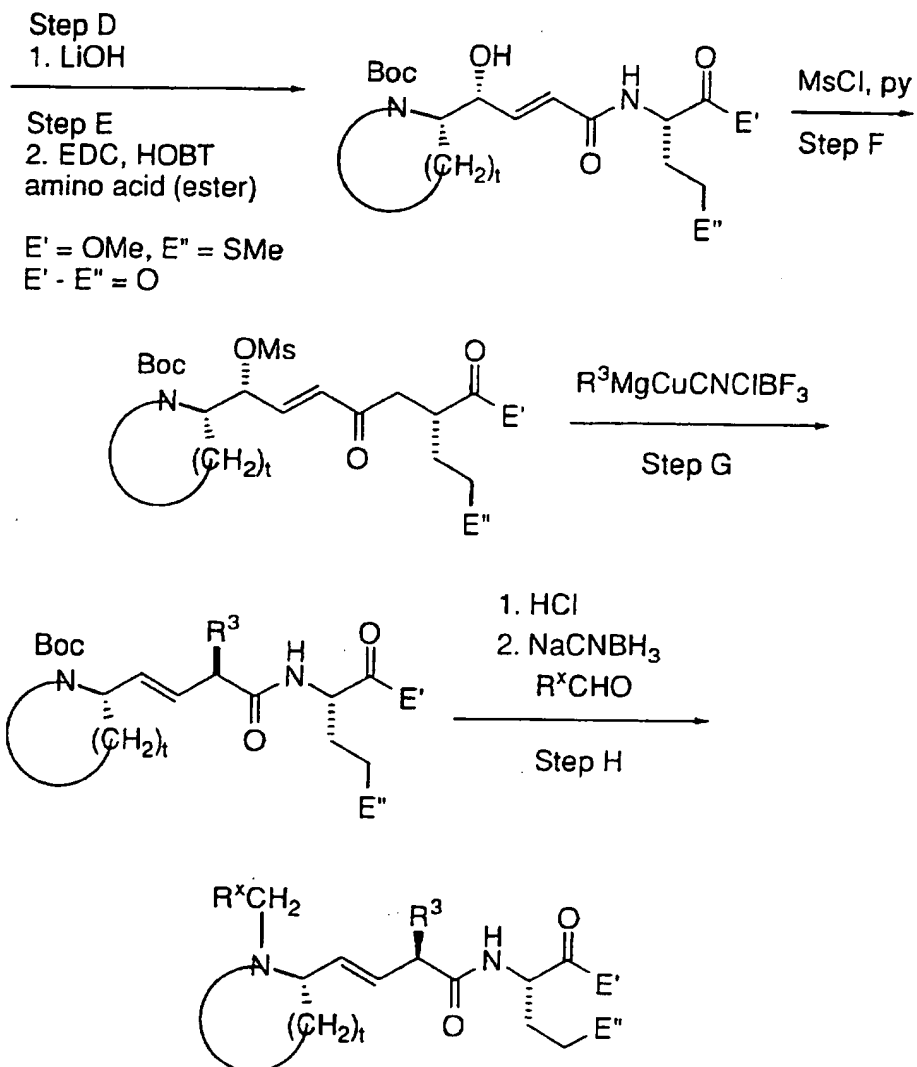
ester hydrolysis, peptide coupling reaction, mesylation, cleavage of peptide protecting groups, reductive alkylation, etc., as may be known in the literature or exemplified in the Experimental Procedure. For simplicity, substituents R^{2a} and R^{2b} on the cyclic amine moiety are not shown. It is, however, understood that the reactions illustrated are also applicable to appropriately substituted cyclic amine compounds. The key reactions are: stereoselective reduction of the Boc-aminoenone to the corresponding syn aminoalcohol (Scheme F, Step B, Part 1), and stereospecific boron trifluoride or zinc chloride activated organo-magnesium, organo-lithio, or organo-zinc copper(I) cyanide S_N2' displacement reaction (Scheme F, Step G). Through the use of optically pure N-Boc amino acids as starting material and these two key reactions, the stereochemistry of the final products is well defined. In Step H of Scheme F, the amino terminus sidechain, designated R^x is incorporated using coupling reaction A and R^xCOOH ; the alkylation reaction C using R^xCHO and a reducing agent; or alkylation reaction C using R^xCH_2XL . Such reactions as described in Step H are described in more detail in Reaction Schemes J-X hereinbelow.

The alkane analogs are prepared in a similar manner by including an additional catalytic hydrogenation step as outlined in Reaction Scheme G.

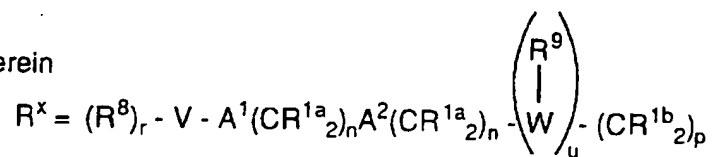
-160-

REACTION SCHEME F

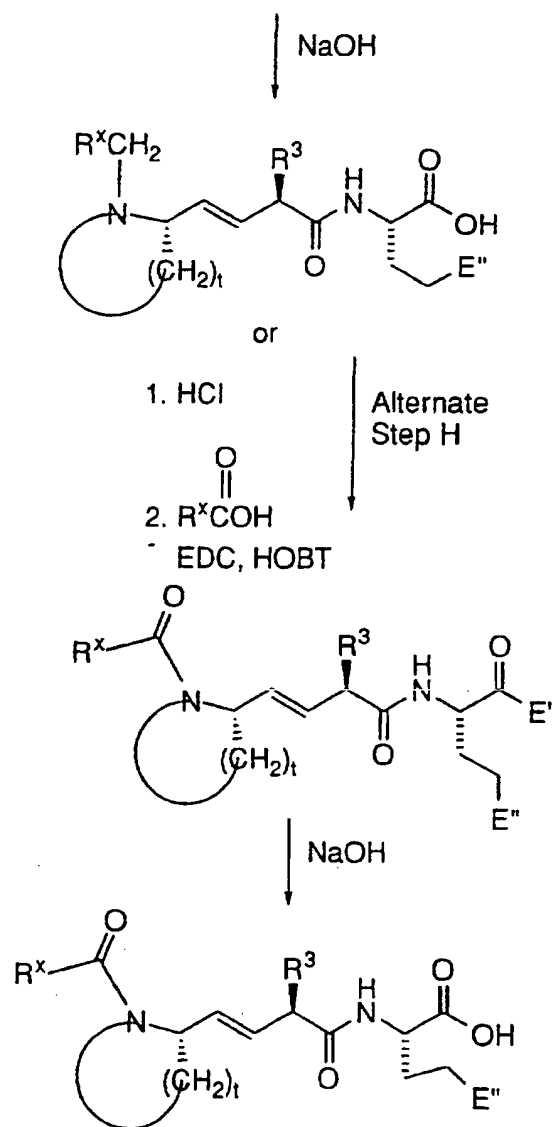
-161-

REACTION SCHEME F (CONT'D)

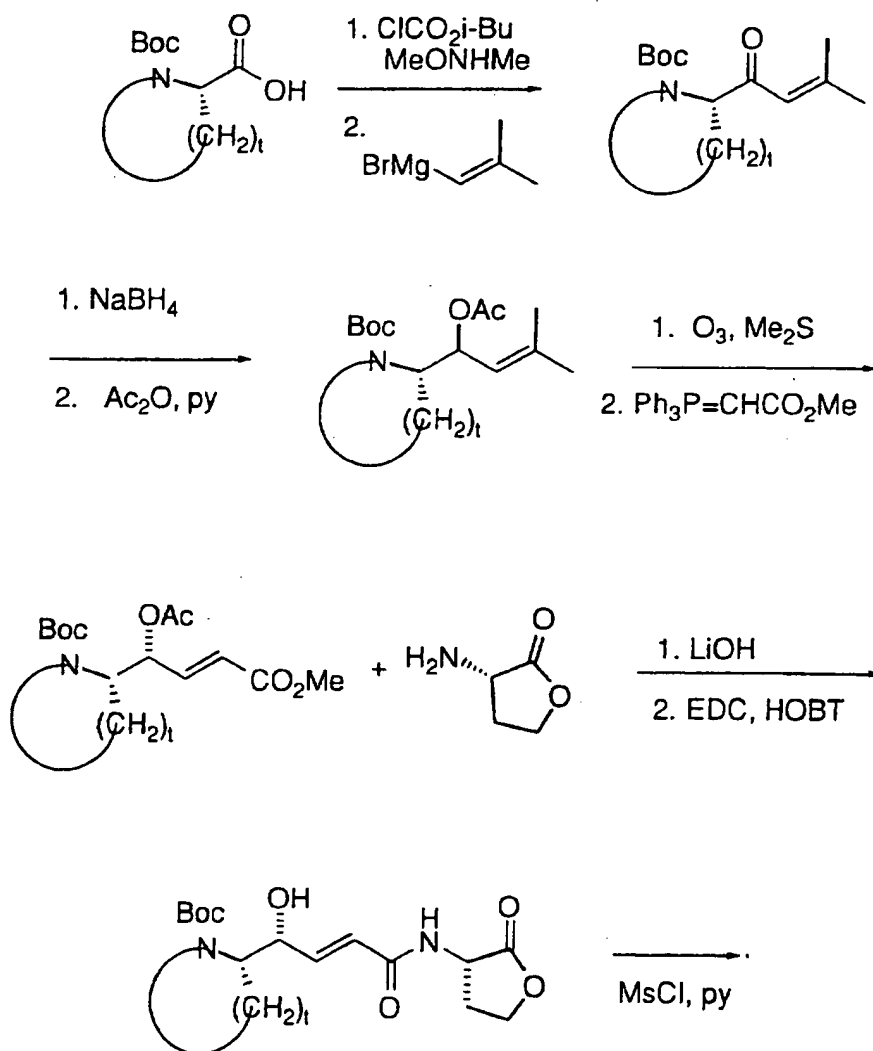
wherein



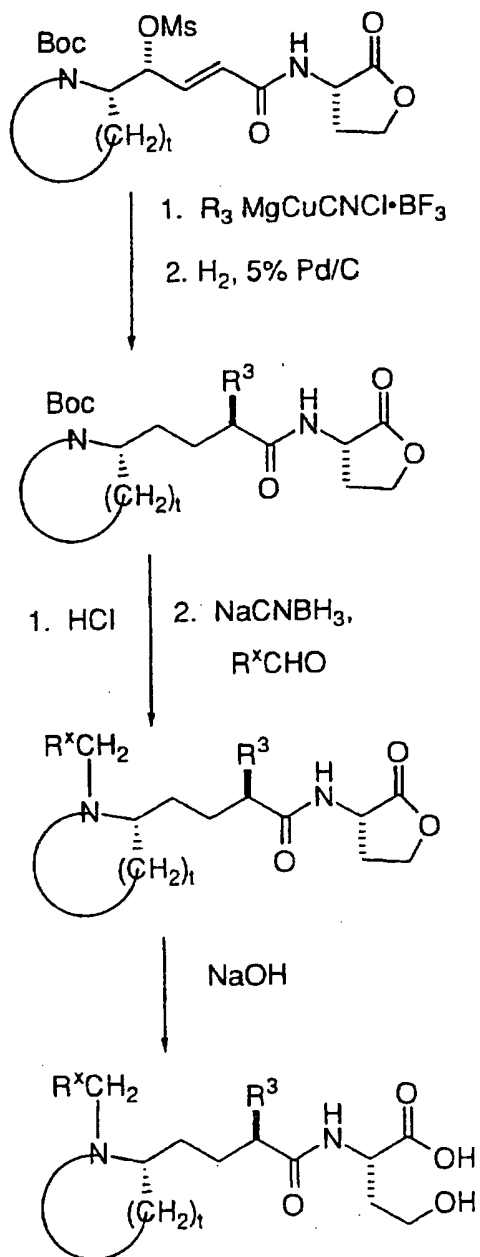
-162-

REACTION SCHEME F (CONT'D)

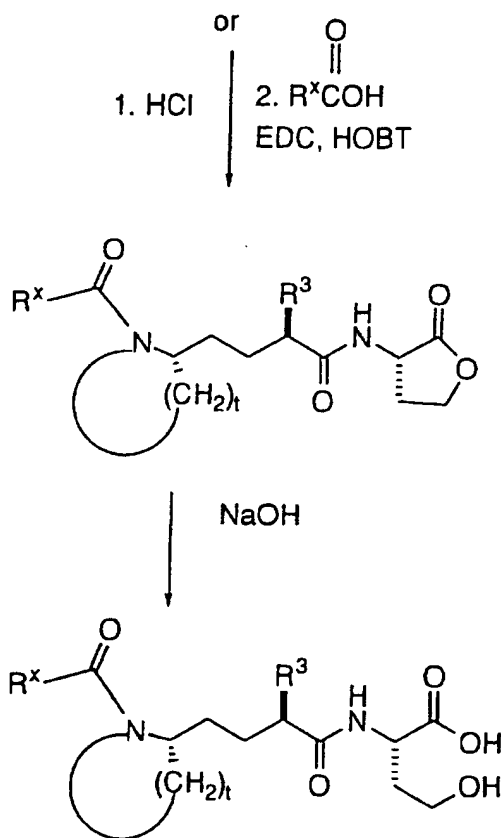
-163-

REACTION SCHEME G

-164-

REACTION SCHEME G (CONT'D)

-165-

REACTION SCHEME G (CONT'D)

- The oxa isostere compounds of this invention are prepared according to the route outlined in Scheme H. An aminoalcohol 1 is acylated with alpha-chloroacetyl chloride in the presence of trialkylamines to yield amide 2. Subsequent reaction of 2 with a deprotonation reagent (e.g., sodium hydride or potassium t-butoxide) in an ethereal solvent such as THF provides morpholinone 3. Alkylation of 3 with R³XL, where XL is a leaving group such as Br-, I- or Cl- in THF/DME (1,2-dimethoxyethane) in the presence of a suitable base, preferably NaHMDS [sodium bis(trimethylsilyl)amide], affords 4, which is retreated with NaHMDS followed by either protonation or the addition of an alkyl halide R⁴X to give 5a or 5b, respectively, as a enantiomeric mixture. Alternatively, 5a can be prepared from 3 via an aldol

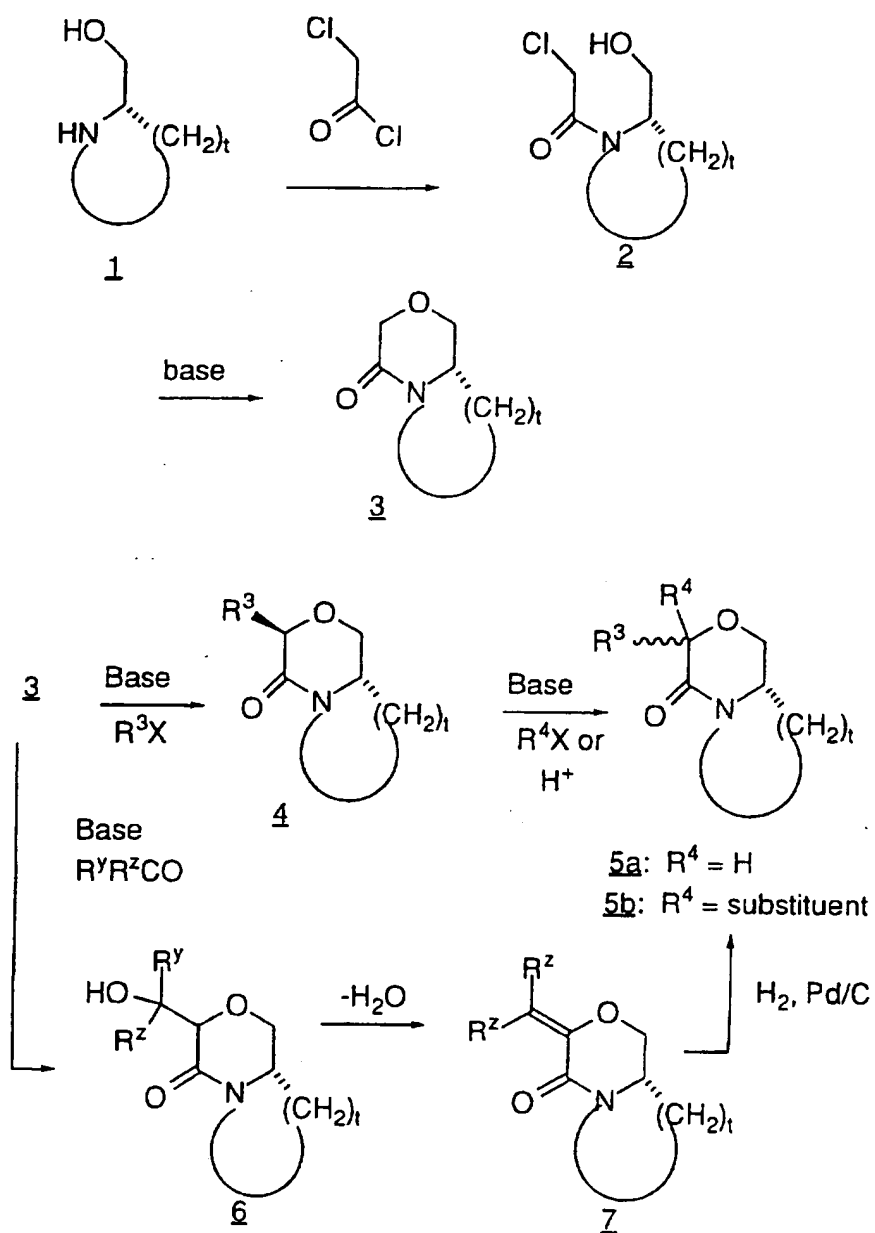
-166-

condensation approach. Namely, deprotonation of 3 with NaHMDS followed by the addition of a carbonyl compound RYR^ZCO gives the adduct 6. Dehydration of 6 can be effected by mesylation and subsequent elimination catalyzed by DBU (1,8-diazabicyclo[5.4.0]
5 undec-7-ene) or the direct treatment of 6 with phosphorus oxychloride in pyridine to give olefin 7. Then, catalytic hydrogenation of 7 yields 5a (wherein -CHRYR^Z constitutes R³). Direct hydrolysis of 5 with lithium hydrogen peroxide in aqueous THF, or aqueous HCl, produces acid 8a. Compound 8a is then derivatized with BOC-ON or BOC
10 anhydride to give 8b. The peptide coupling of acid 8b with either an alpha-aminolactone (e.g., homoserine lactone, etc.) or the ester of an amino acid is carried out under the conditions exemplified in the previously described references to yield derivative 9. Treatment
15 of 9 with gaseous hydrogen chloride gives 10, which undergoes further elaboration as described in Reaction Schemes J- hereinbelow.

An alternative method for the preparation of the prolyl oxa isostere (compounds 23 and 24) is shown in Scheme H-1. Referring to Scheme H-1, the aminoalcohol 1 is protected with trifluoroacetic anhydride and the blocked compound 15 treated with
20 diphenyl disulfide in the presence of tributylphosphine to provide the thioether 16. Chlorination of compound 16 provides compound 17 which can be reacted with the appropriate carboxylic acid alcohol in the presence of silver perchlorate and tin (II) chloride, to afford the mixed acetal 18. Removal of the phenylmercapto moiety with Raney nickel
25 provides compound 19. Compound 19 is doubly deprotected, then selectively BOC protected to provide the acid 20, which undergoes the steps previously described for incorporating terminal amino acid. Still another alternative method for the preparation of the prolyl oxa isostere (compounds 23 and 24) is described in the literature [Ruth E.
30 TenBrink, J. Org. Chem., 52, 418-422 (1987)].

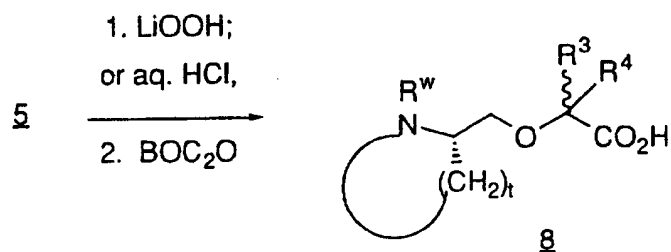
-167-

SCHEME H

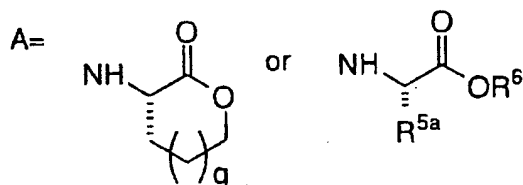
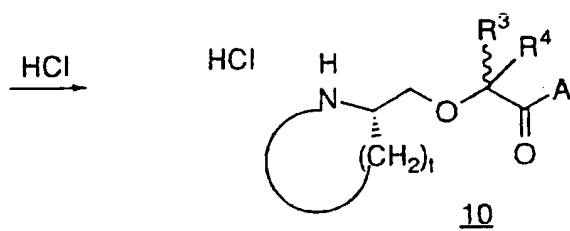
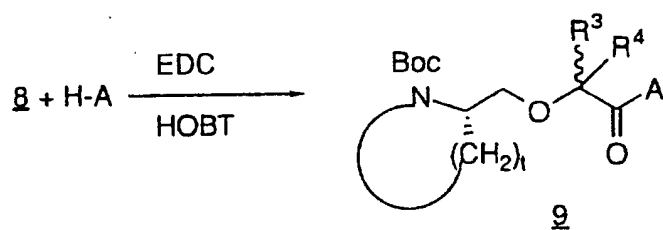


-168-

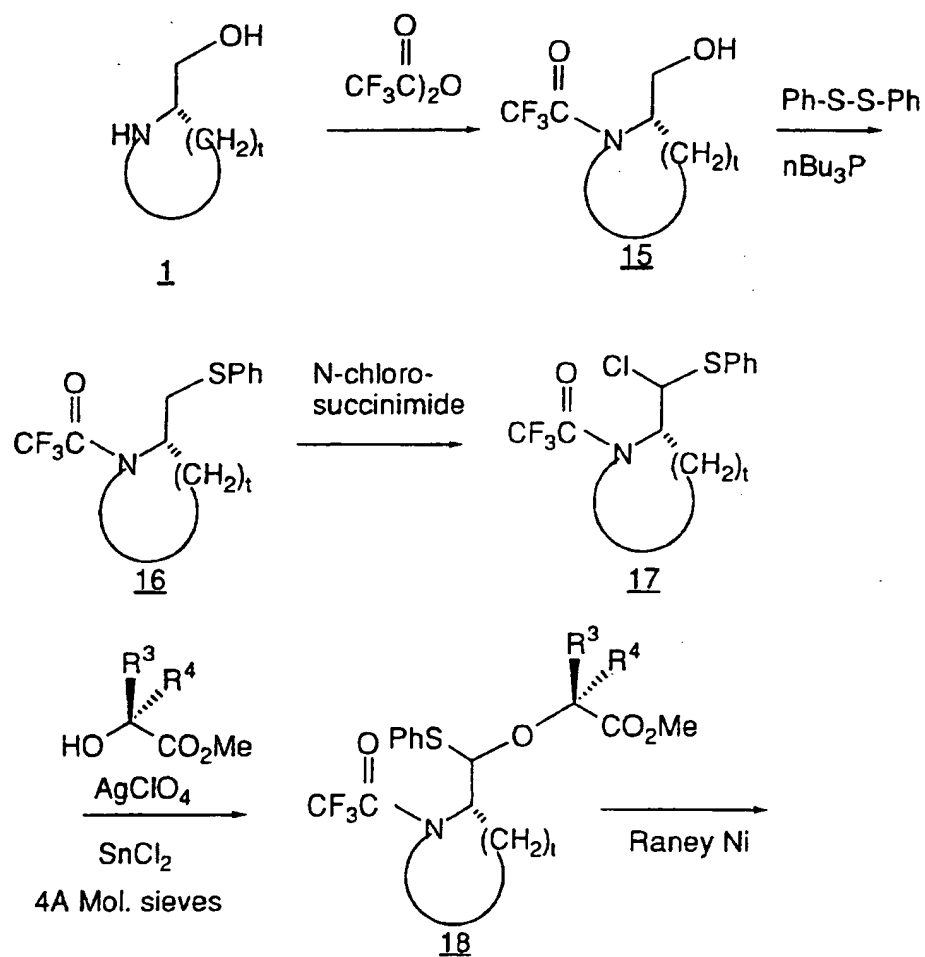
SCHEME H (CONT'D)



a, $R^w = \text{H}$
 b, $R^w = \text{BOC}$

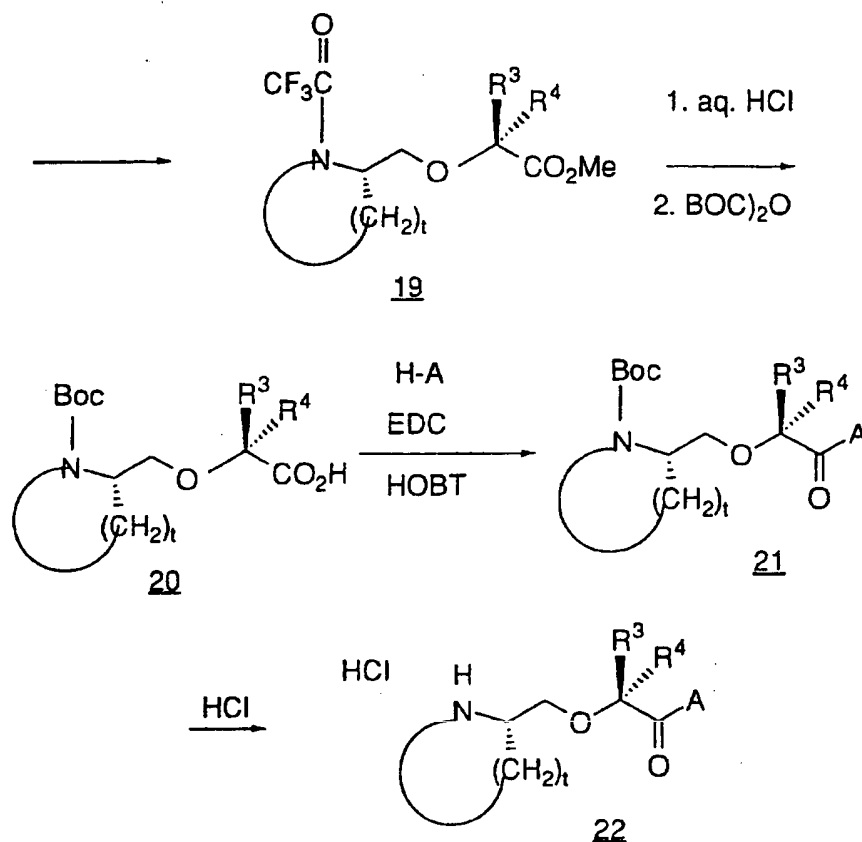


-169-

SCHEME H-1

-170-

SCHEME H-1 (CONT'D)

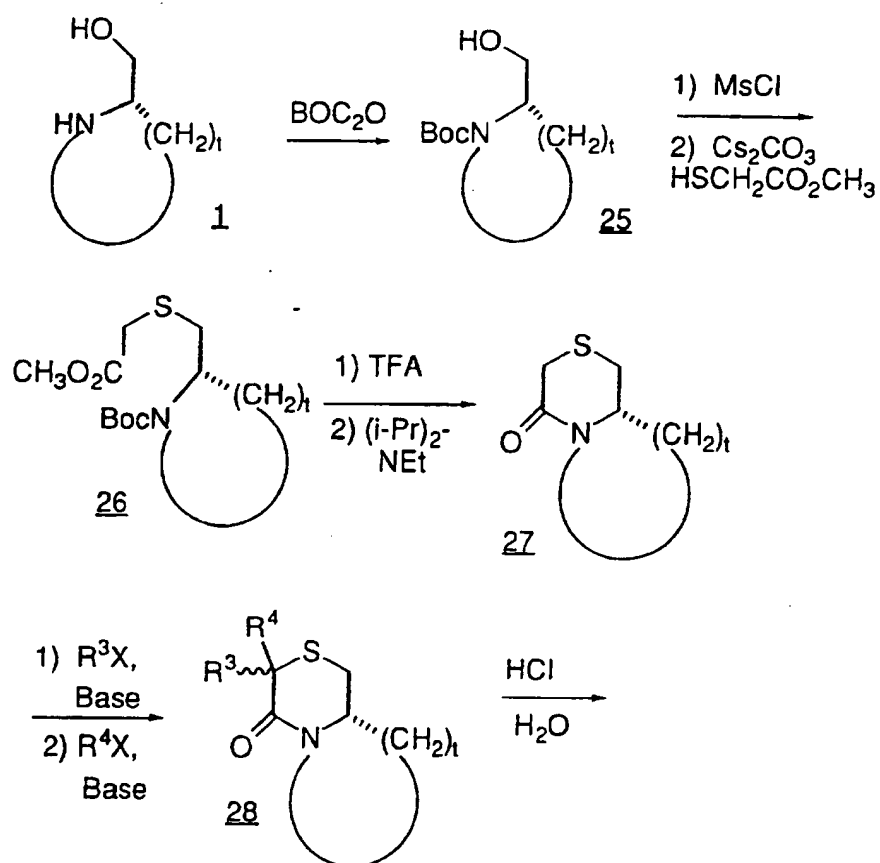


- The thia, oxothia and dioxothia isostere compounds of this invention are prepared in accordance to the route depicted in Scheme I.
- 5 Aminoalcohol 1 is derivatized with BOC_2O to give 25. Mesylation of 25 followed by reaction with methyl alpha-mercaptoacetate in the presence of cesium carbonate gives sulfide 26. Removal of the Boc group in 26 with TFA followed by neutralization with di-isopropyl-ethylamine leads to lactam 27. Sequential alkylation of 27 with the alkyl
- 10 halides R^3X and R^4X in THF/DME using NaHDMS as the deprotonation reagent produces 28. Hydrolysis of 28 in hydro-chloride to yield 29a, which is derivatized with Boc anhydride to yield 29b. The coupling of 29b with an alpha-aminolactone (e.g., homoserine lactone, etc.) or the ester of an amino acid is carried out under conventional conditions as

-171-

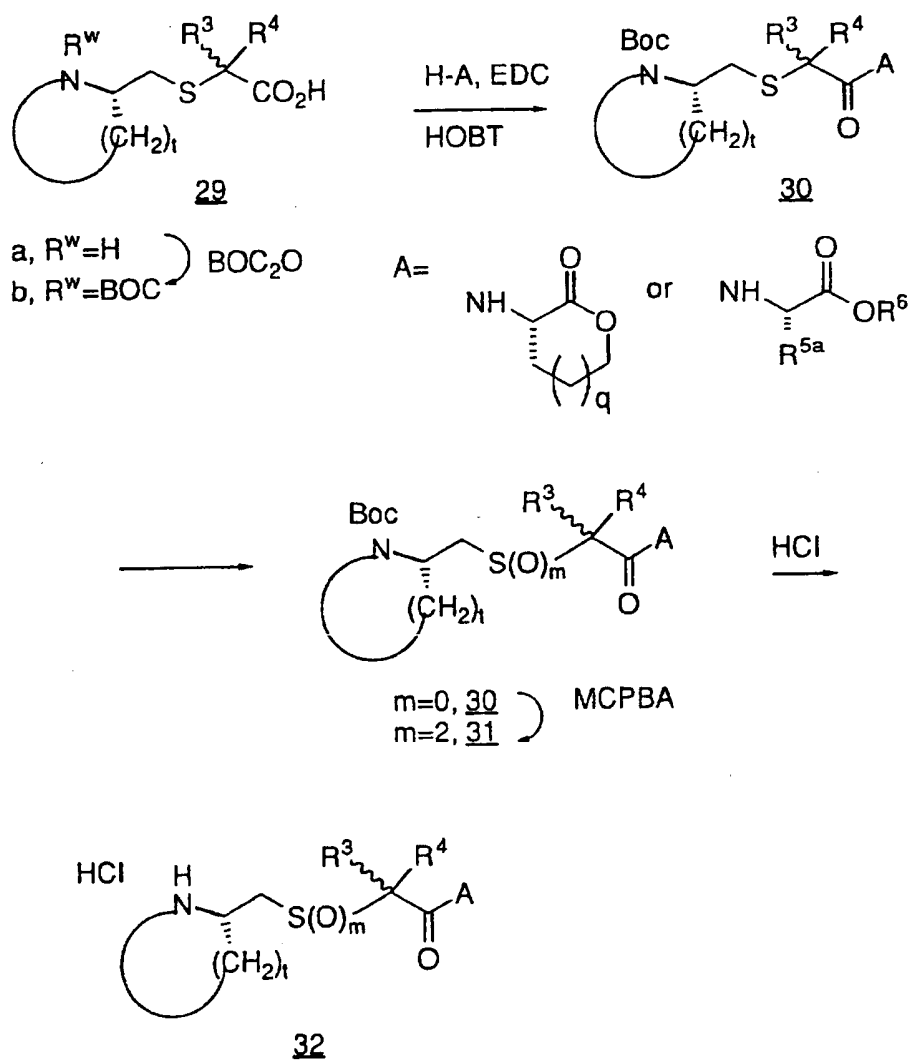
exemplified in the previously described references to afford 30. Sulfide 30 is readily oxidized to sulfone 31 by the use of MCPBA (m-chloroperoxybenzoic acid). The N-BOC group of either 30 or 31 is readily removed by treatment with gaseous hydrogen chloride.

5

SCHEME I

-172-

SCHEME 1 (Continued)



5

 $m = 0 \text{ or } 2$

Reaction Schemes J - R illustrate reactions wherein the non-sulfhydryl-containing moiety at the N-terminus of the compounds of the instant invention is attached to the fully elaborated cyclic amino peptide unit, prepared as described in Reaction Schemes A-I. It is understood

-173-

that the reactions illustrated may also be performed on a simple cyclic amino acid, which may then be further elaborated utilizing reactions described in Reaction Schemes A- I to provide the instant compounds.

The intermediates whose synthesis are illustrated in

- 5 Reaction Schemes A-I can be reductively alkylated with a variety of aldehydes, such as V, as shown in Reaction Scheme J. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75, from the appropriate amino acid (Reaction Scheme F).
- 10 The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product VI can be deprotected with trifluoroacetic acid in methylene chloride to give the final compounds
- 15 VII. The final product VII is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine VII can further be selectively protected to obtain VIII, which can subsequently be reductively alkylated with a second aldehyde to obtain IX. Removal of the protecting group, and
- 20 conversion to cyclized products such as the dihydroimidazole XI can be accomplished by literature procedures.

- Alternatively, the protected cyclic aminopeptidyl intermediate can be reductively alkylated with other aldehydes such as 1-trityl-4-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give
- 25 products such as XII (Reaction Scheme K). The trityl protecting group can be removed from XII to give XIII, or alternatively, XII can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XIV. Alternatively, the dipeptidyl analog intermediate can be acylated or sulfonylated by standard techniques.

- 30 The imidazole acetic acid XV can be converted to the protected acetate XVII by standard procedures, and XVII can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XVIII. Hydrolysis and reaction with the protected dipeptidyl analog

-174-

intermediate in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XIX.

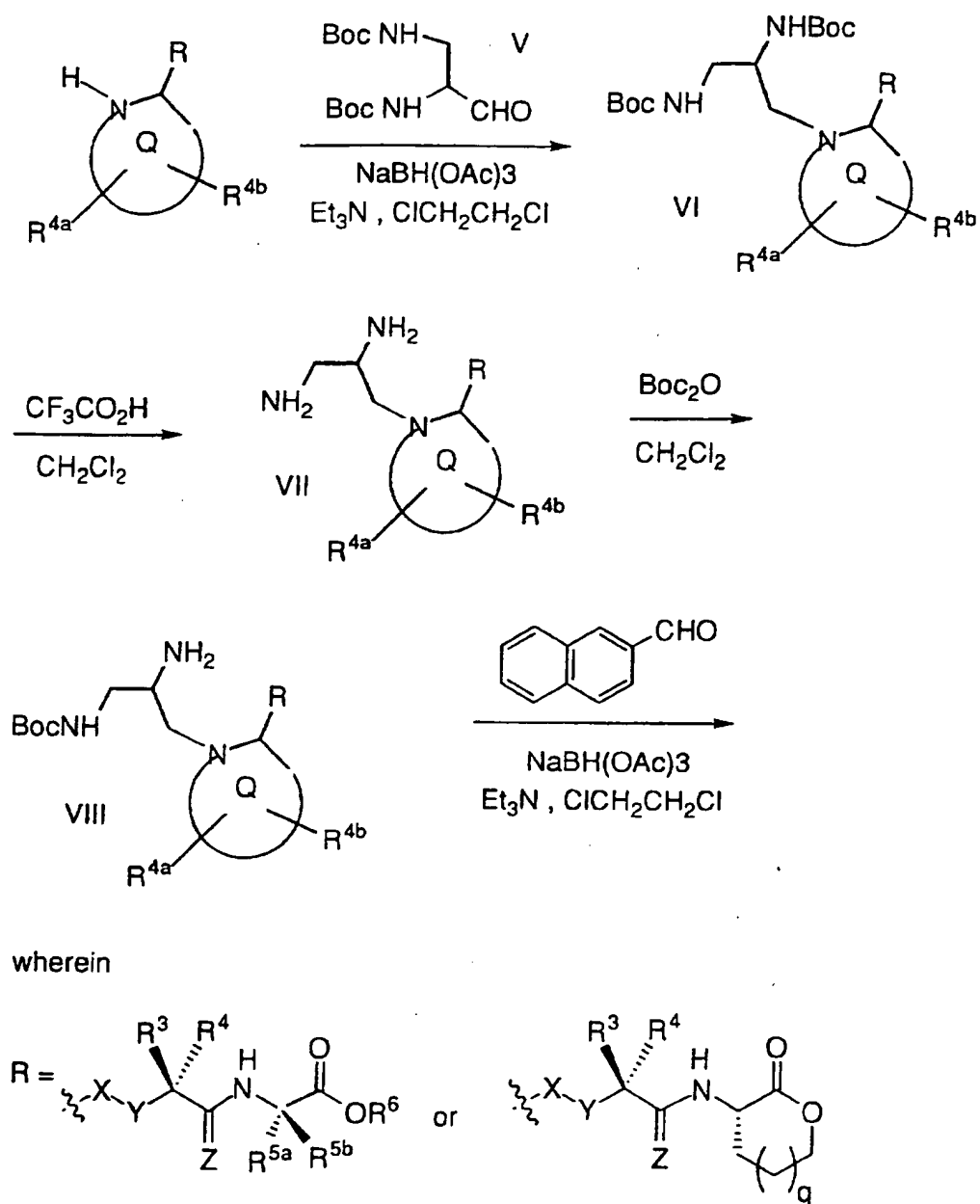
If the protected dipeptidyl analog intermediate is
5 reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XX in Reaction Scheme N, the protecting groups can be subsequently removed to unmask the hydroxyl group (Reaction Schemes N, P). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety
10 of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIV. In addition, the fully deprotected amino alcohol XXV can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXVI (Reaction Scheme P), or tertiary amines.

15 The Boc protected amino alcohol XXII can also be utilized to synthesize 2-aziridinylmethylpiperazines such as XXVII (Reaction Scheme Q). Treating XXII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXVII. The aziridine may be reacted in the presence of a
20 nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXVIII.

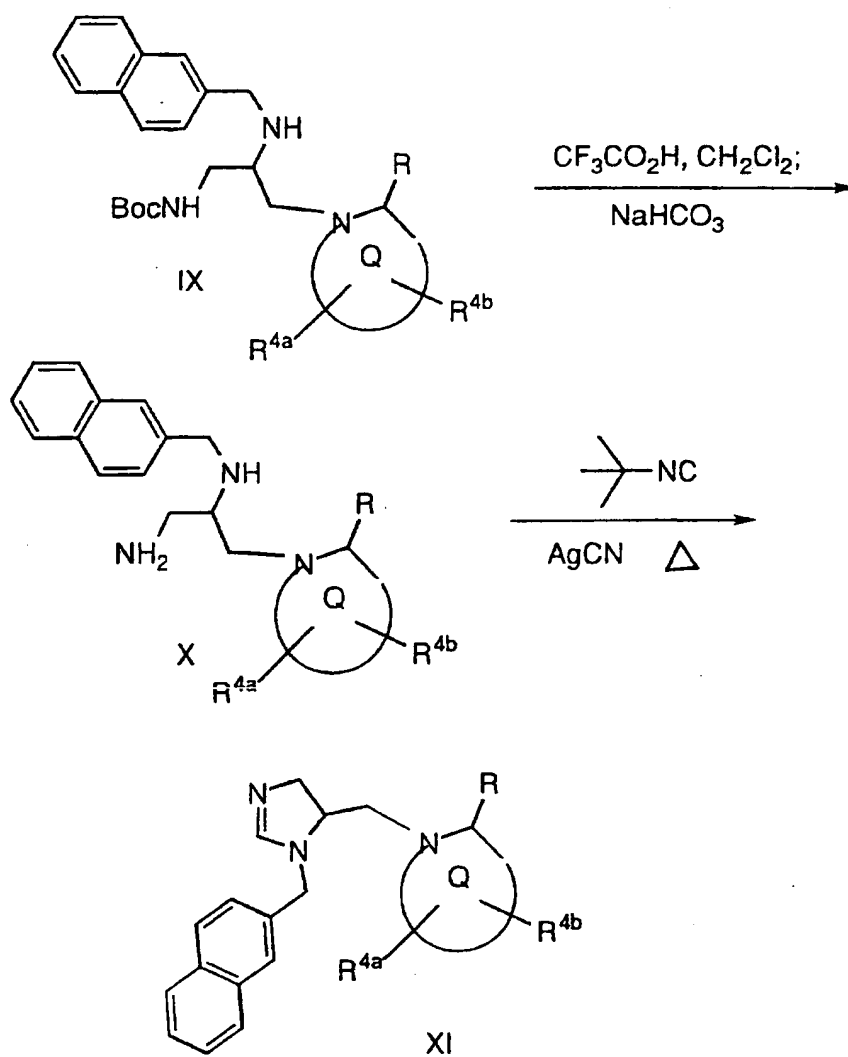
In addition, the protected dipeptidyl analog intermediate can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain
25 compounds such as XXXIV, as shown in Reaction Scheme R. When R' is an aryl group, XXXIV can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XXXV. Alternatively, the amine protecting group in XXXIV can be removed, and O-alkylated phenolic amines such as XXXVI produced.

30

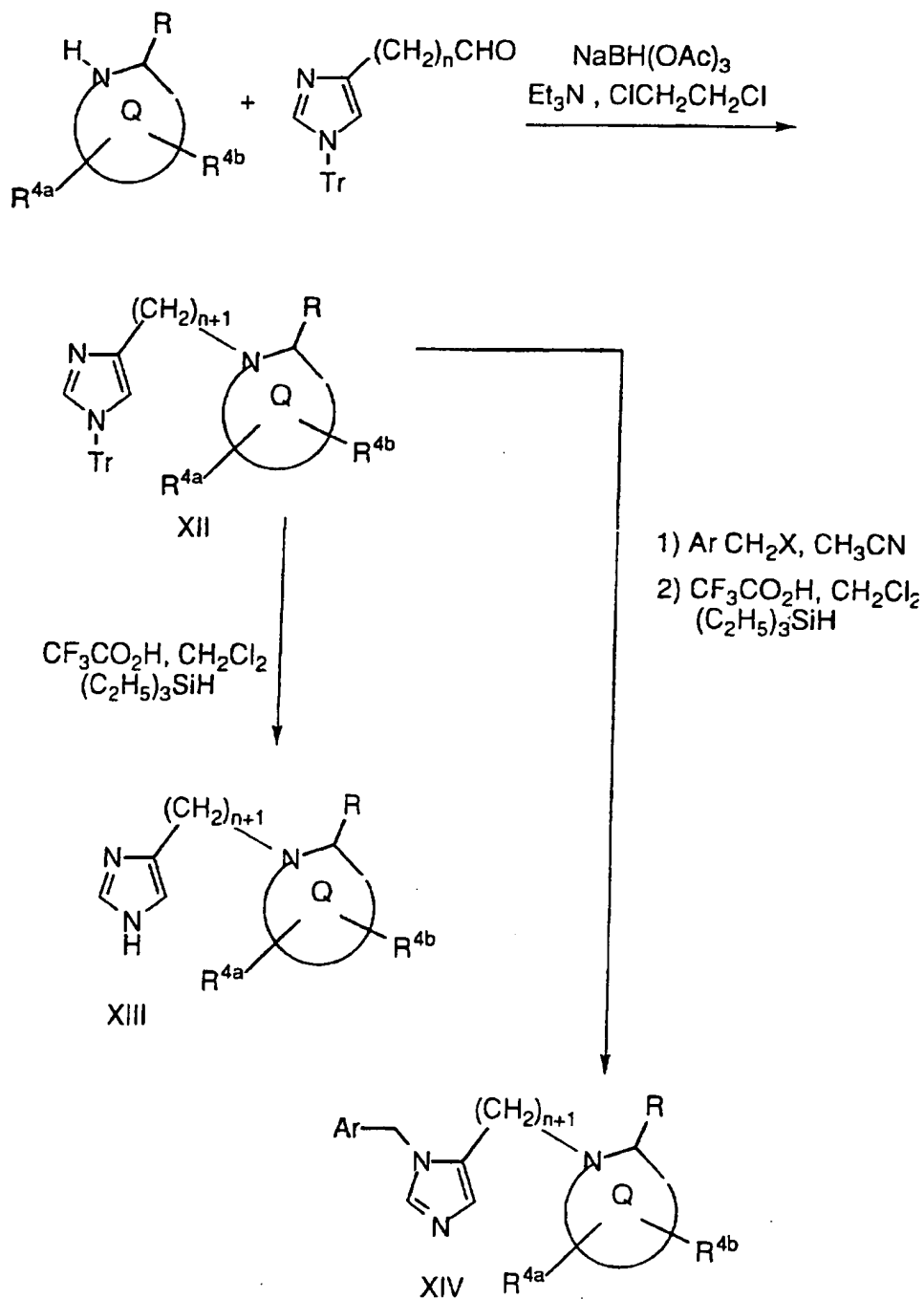
-175-

REACTION SCHEME J

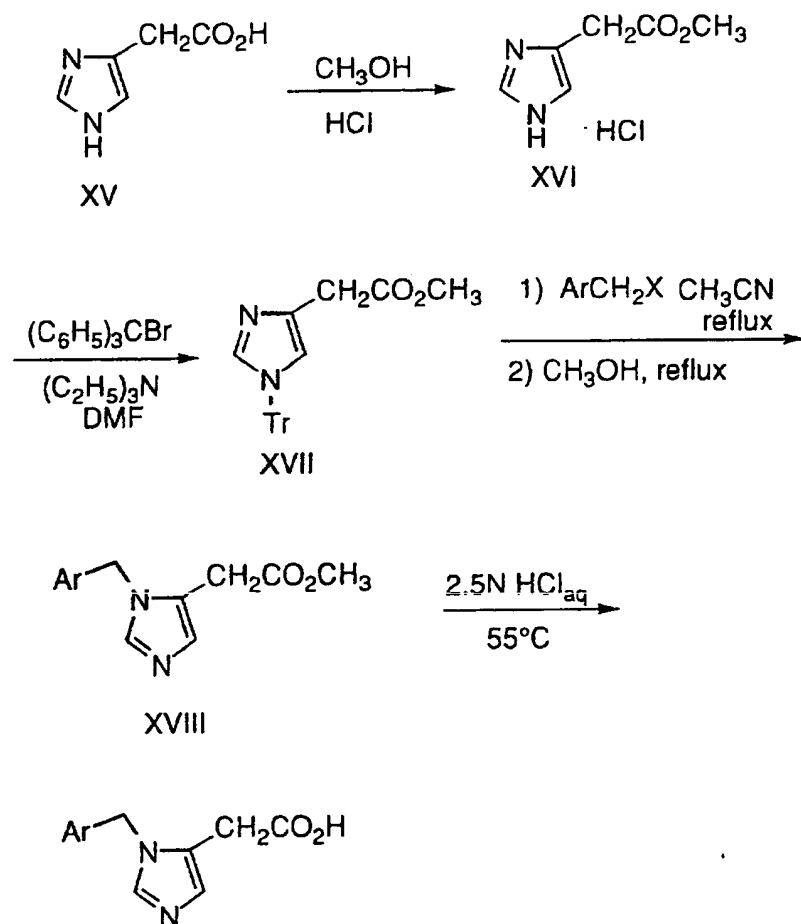
-176-

REACTION SCHEME J (continued)

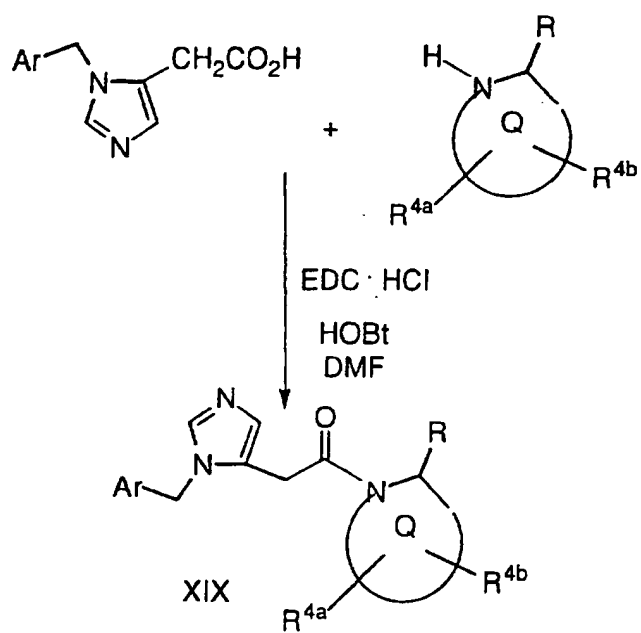
-177-

REACTION SCHEME K

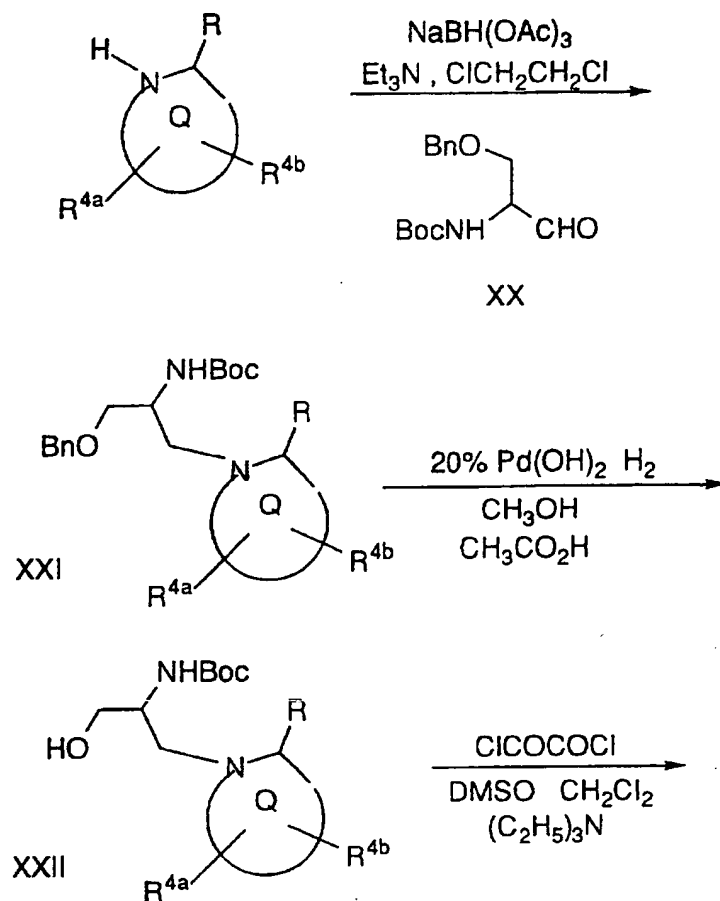
-178-

REACTION SCHEME L

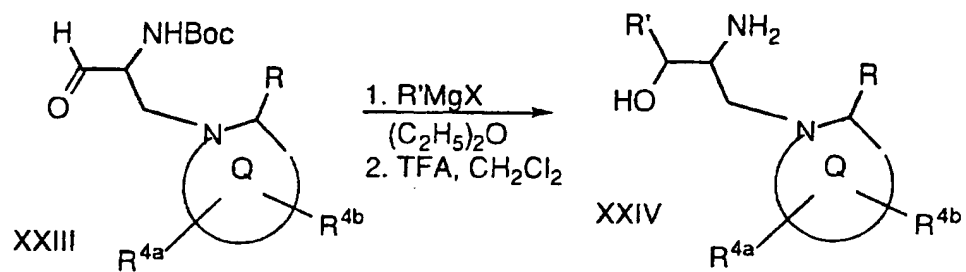
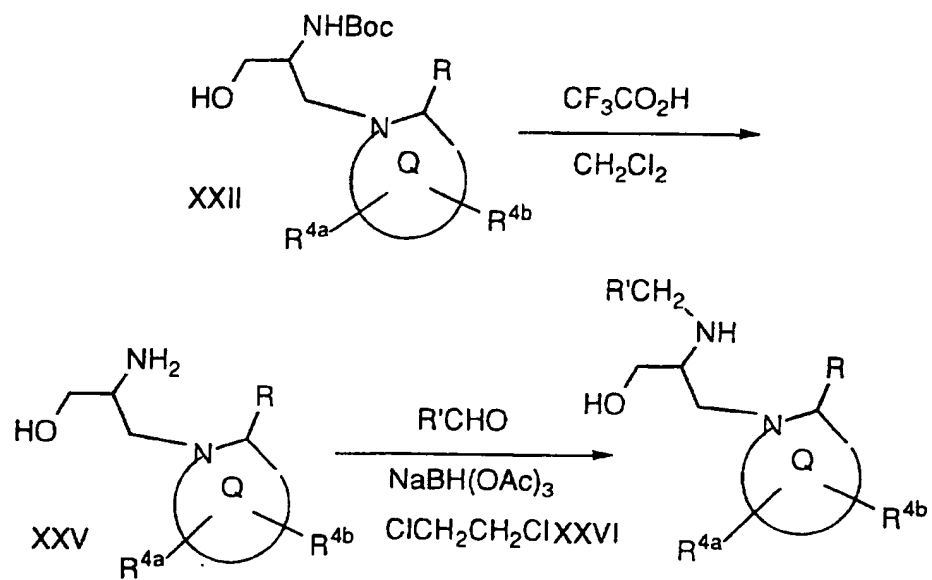
-179-

REACTION SCHEME M

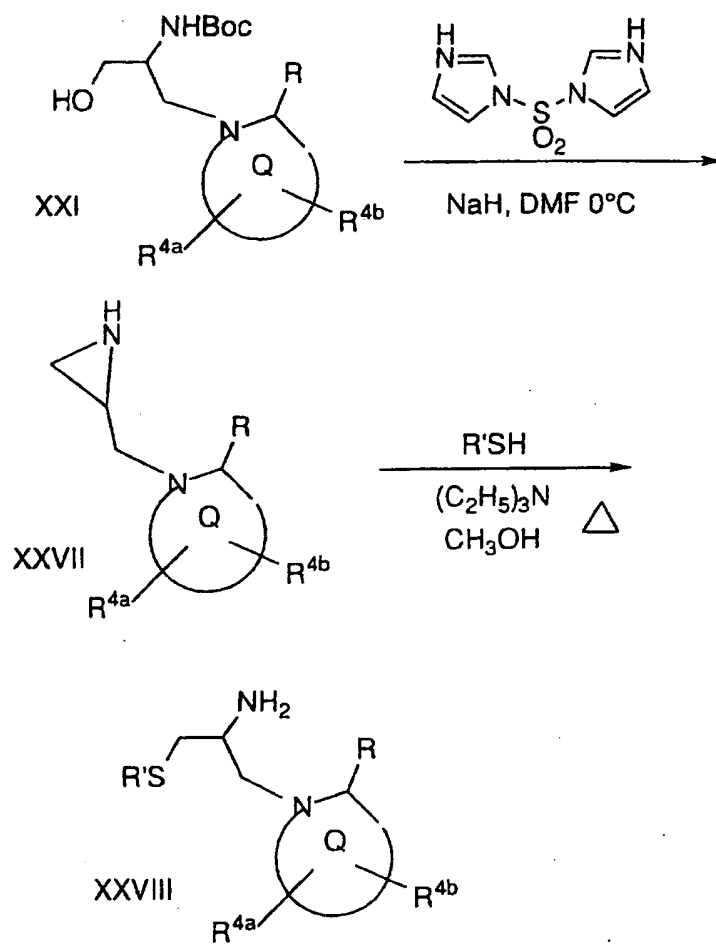
-180-

REACTION SCHEME N

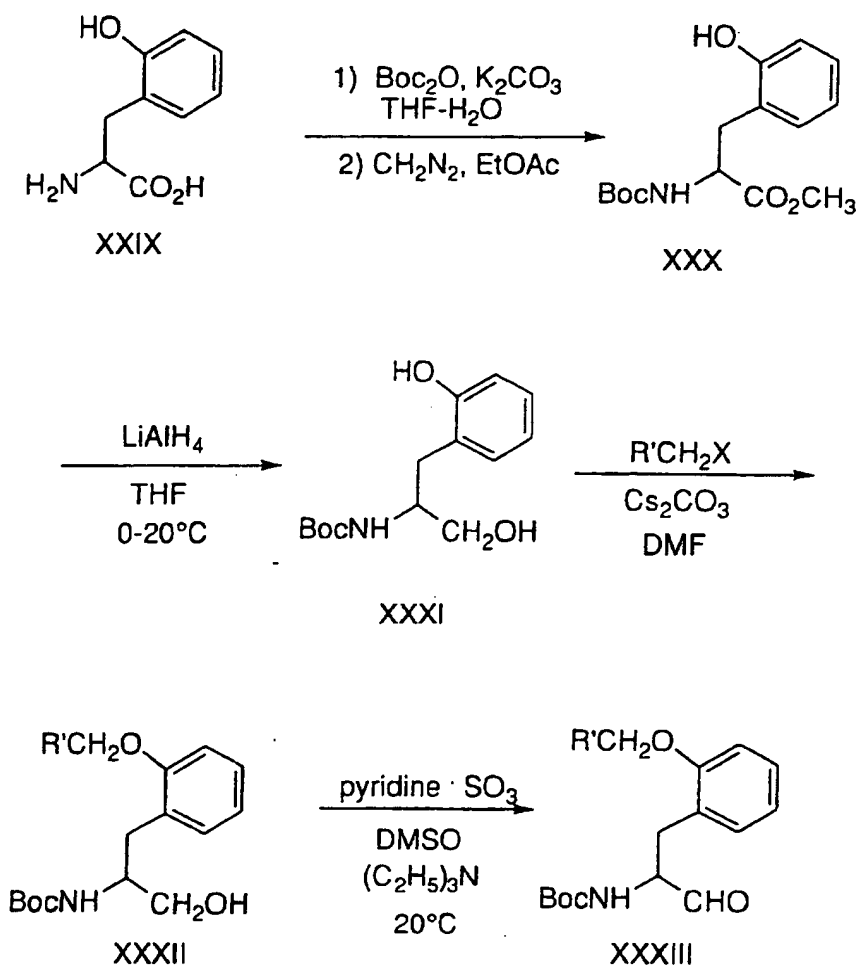
-181-

REACTION SCHEME N (continued)REACTION SCHEME P

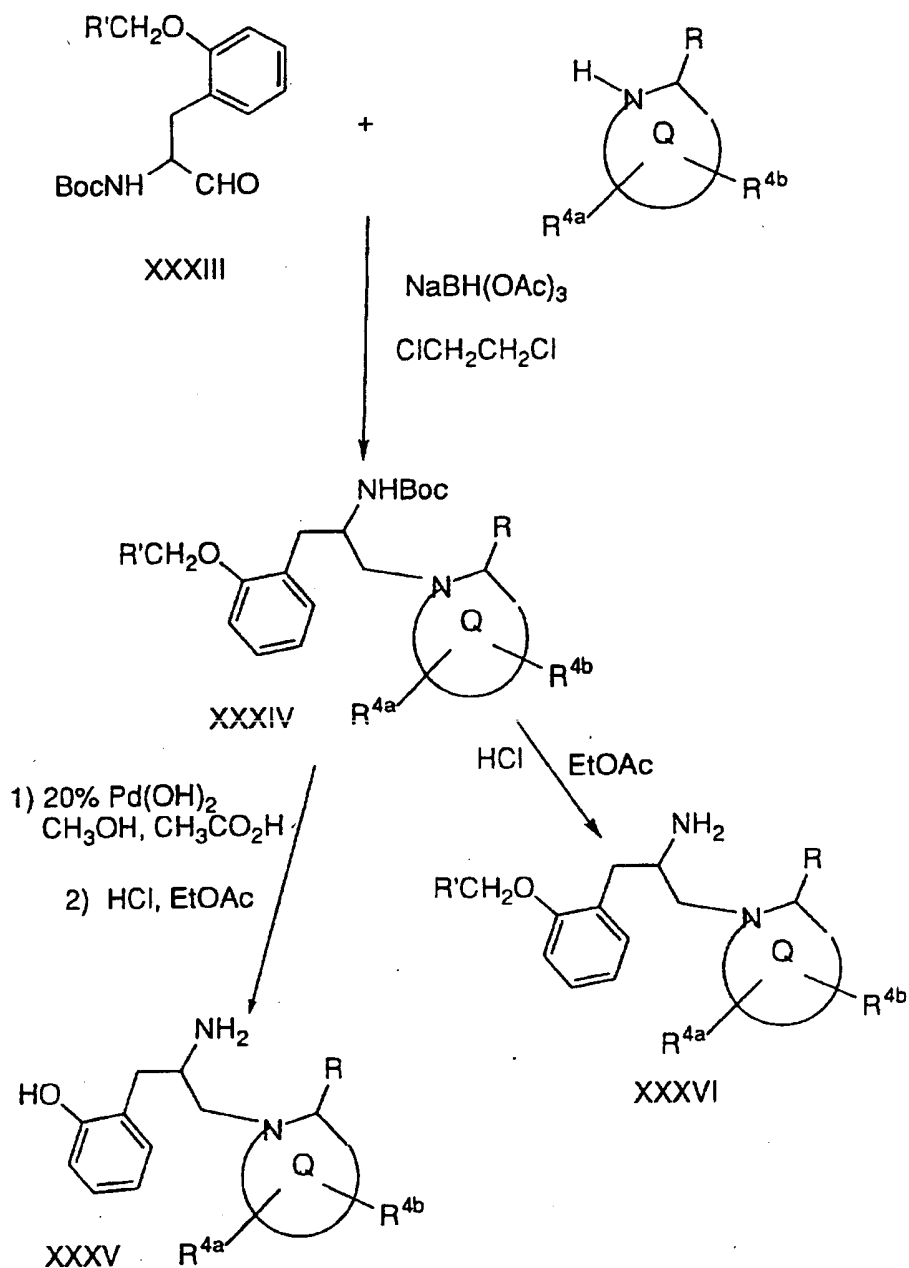
-182-

REACTION SCHEME Q

-183-

REACTION SCHEME R

-184-

REACTION SCHEME R (continued)

The intermediates whose synthesis are illustrated in Reaction Schemes A and C can be reductively alkylated with a variety

-185-

of aldehydes, such as I, as shown in Reaction Scheme F. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75, from the appropriate amino acid (Reaction Scheme F). The

5 reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product II can be deprotected to give the final compounds III with trifluoroacetic acid in methylene chloride.

10 The final product III is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine III can further be selectively protected to obtain IV, which can subsequently be reductively alkylated with a second aldehyde to obtain V. Removal of the protecting group, and conversion to

15 cyclized products such as the dihydroimidazole VII can be accomplished by literature procedures.

Alternatively, the protected dipeptidyl analog intermediate can be reductively alkylated with other aldehydes such as 1-trityl-4-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products

20 such as VIII (Alternative Reaction Scheme G). The trityl protecting group can be removed from VIII to give IX, or alternatively, VIII can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole X. Alternatively, the dipeptidyl analog intermediate can be acylated or sulfonylated by standard techniques.

25 The imidazole acetic acid XI can be converted to the acetate XIII by standard procedures, and XIII can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XIV (Alternative Reaction Scheme H). Hydrolysis and reaction with the protected

30 dipeptidyl analog intermediate in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XV.

If the protected dipeptidyl analog intermediate is reductively alkylated with an aldehyde which also has a protected

-186-

hydroxyl group, such as **XVI** in Reaction Scheme I, the protecting groups can be subsequently removed to unmask the hydroxyl group (Reaction Schemes I, J). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as **XX**. In addition, the fully deprotected amino alcohol **XXI** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **XXII** (Reaction Scheme K), or tertiary amines.

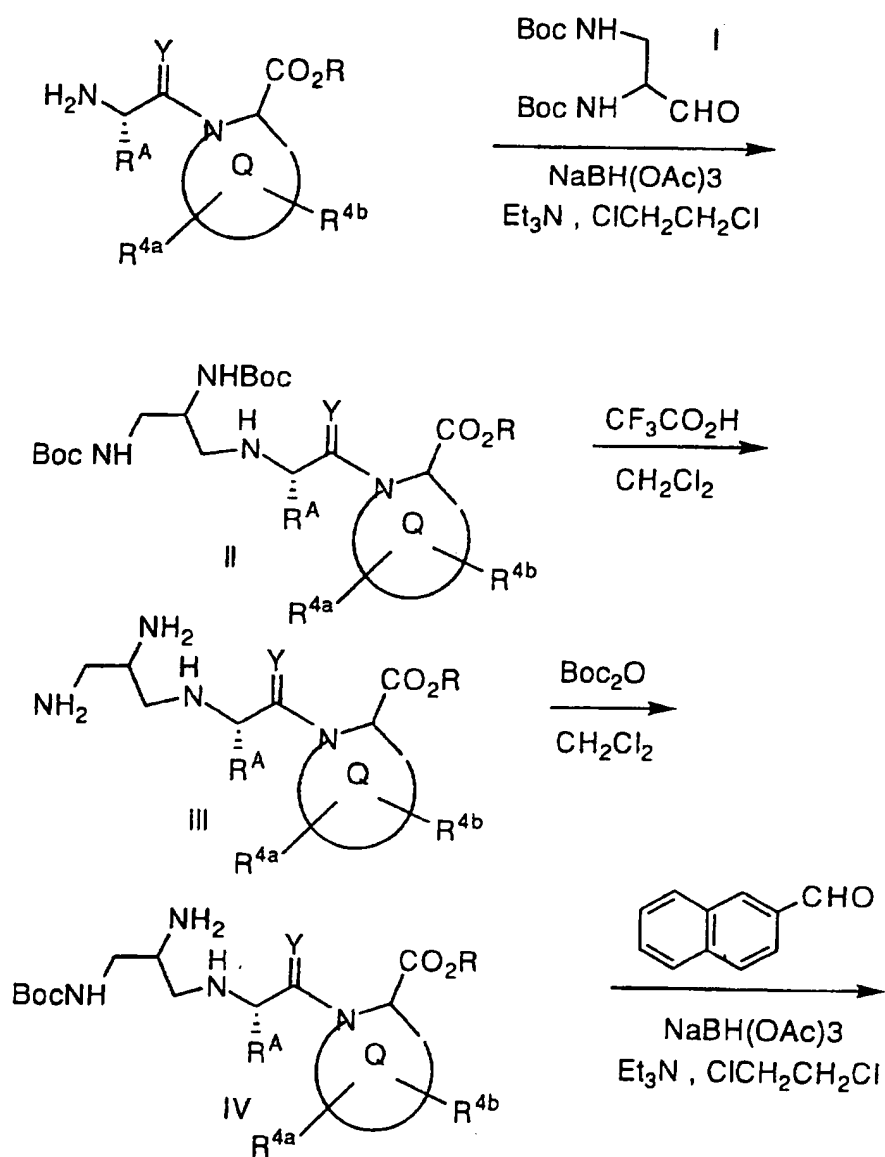
10 The Boc protected amino alcohol **XVIII** can also be utilized to synthesize 2-aziridinylmethylpiperazines such as **XXIII** (Reaction Scheme L). Treating **XVIII** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine **XXIII**. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **XXIV**.

15 In addition, the protected dipeptidyl analog intermediate can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **XXX**, as shown in Reaction Scheme M. When **R'** is an aryl group, **XXX** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **XXXI**. Alternatively, the amine protecting group in **XXX** can be removed, and O-alkylated phenolic amines such as **XXXII** produced.

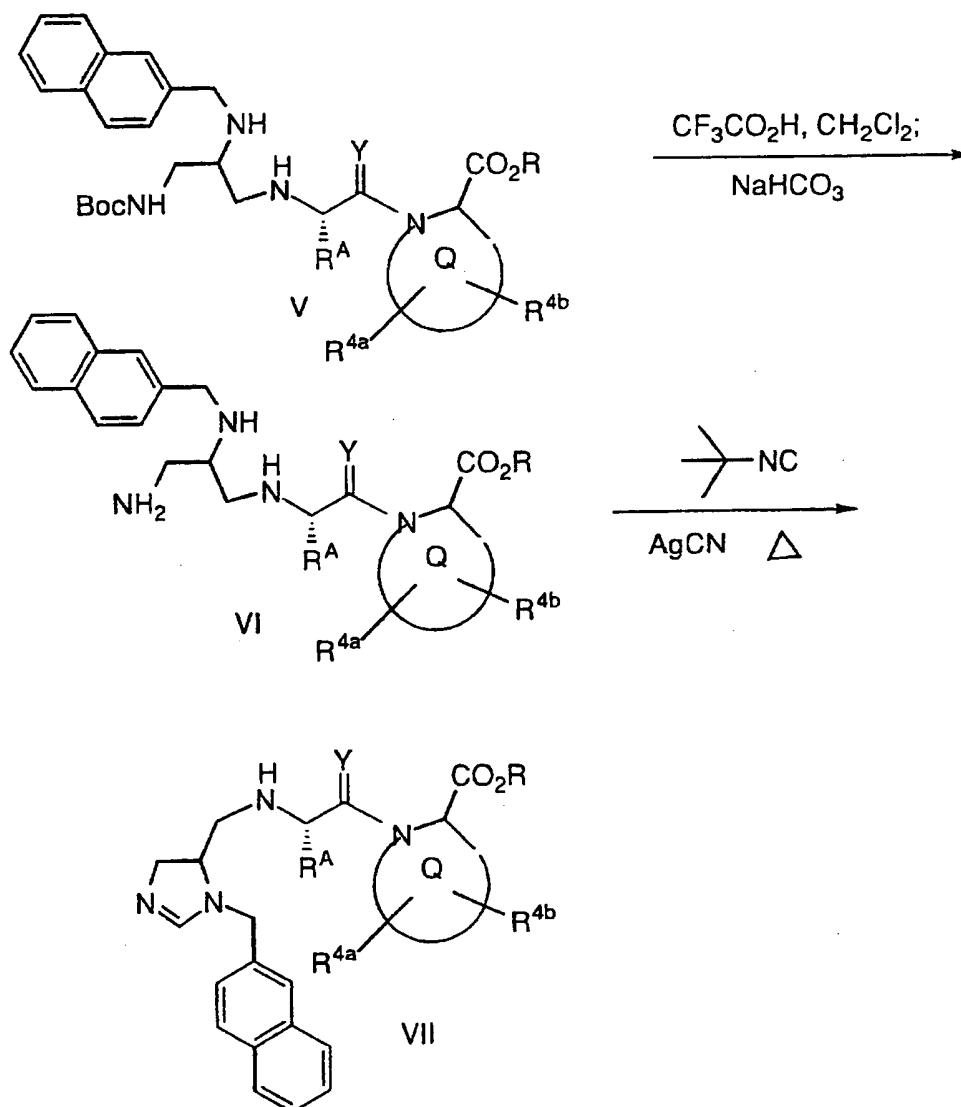
25 Similar procedures as are illustrated in Reaction Schemes F-M may be employed using other peptidyl analog intermediates such as those whose synthesis is illustrated in Reaction Schemes B - E.

-187-

ALTERNATE REACTION SCHEME F FOR
COMPOUNDS (II-h) THROUGH (II-o)

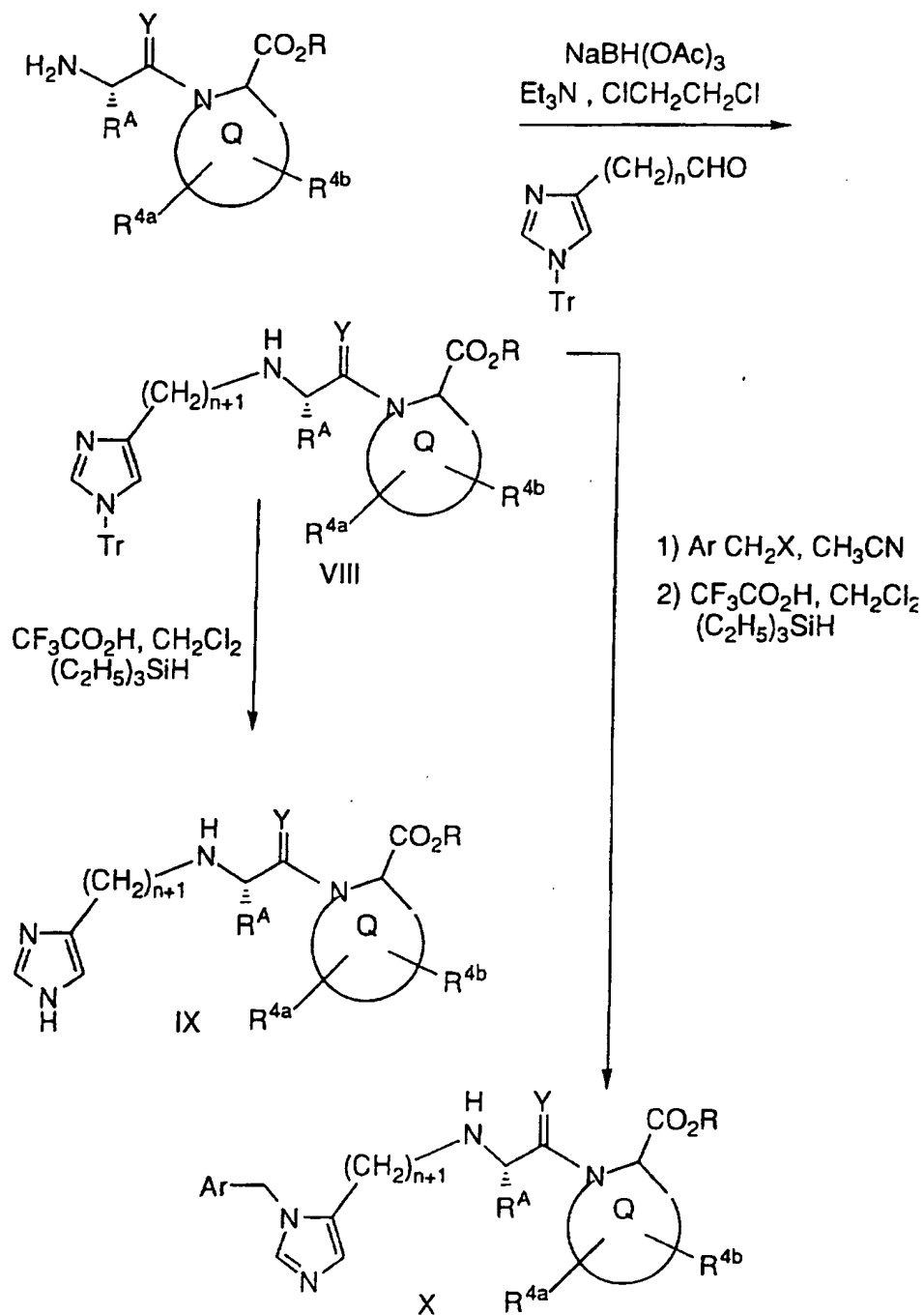


-188-

ALTERNATE REACTION SCHEME F (continued)

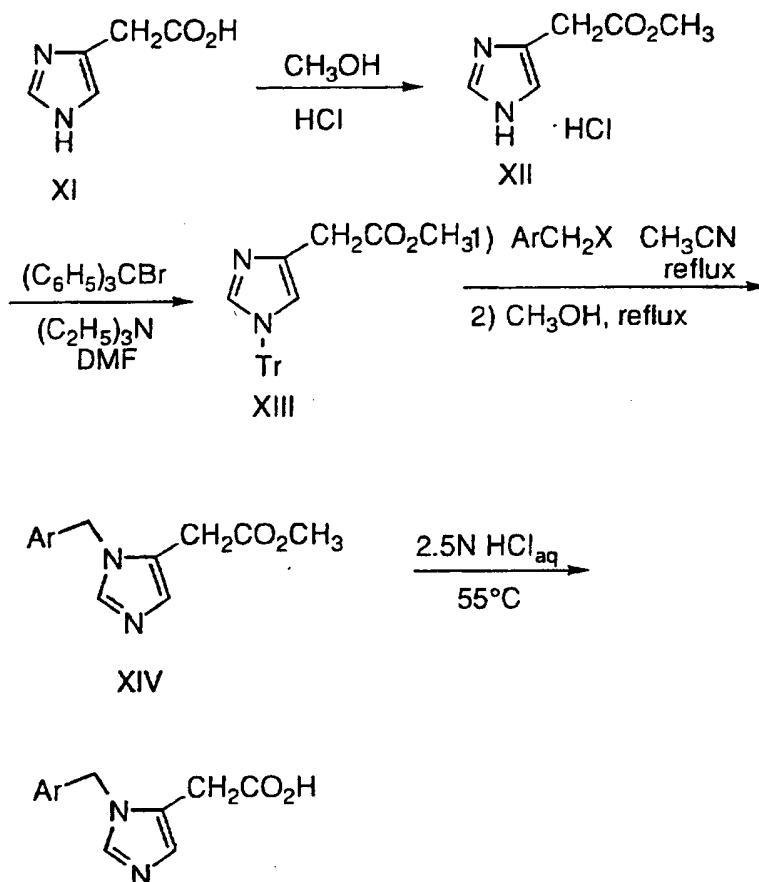
-189-

ALTERNATE REACTION SCHEME G FOR
COMPOUNDS (II-h) THROUGH (II-o)



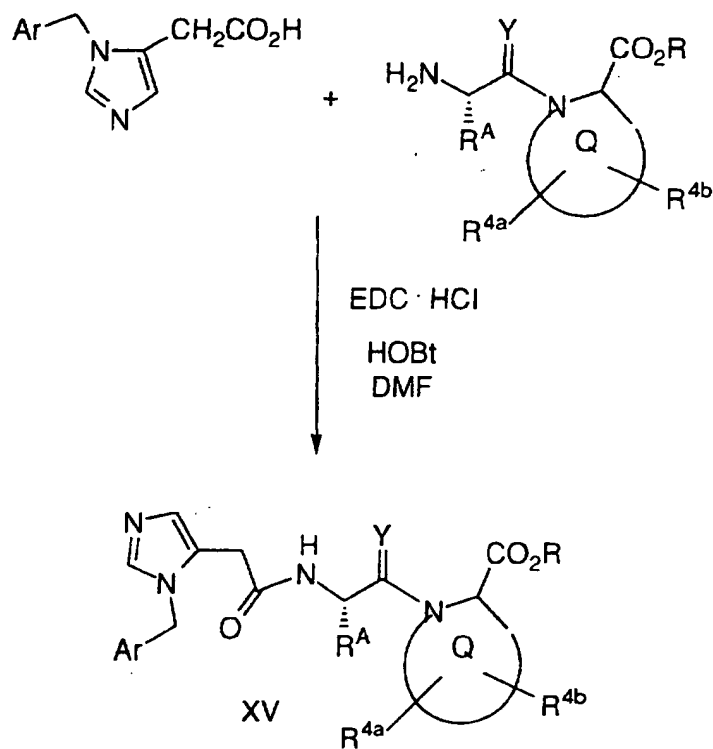
-190-

ALTERNATE REACTION SCHEME H FOR
COMPOUNDS (II-h) THROUGH (II-o)



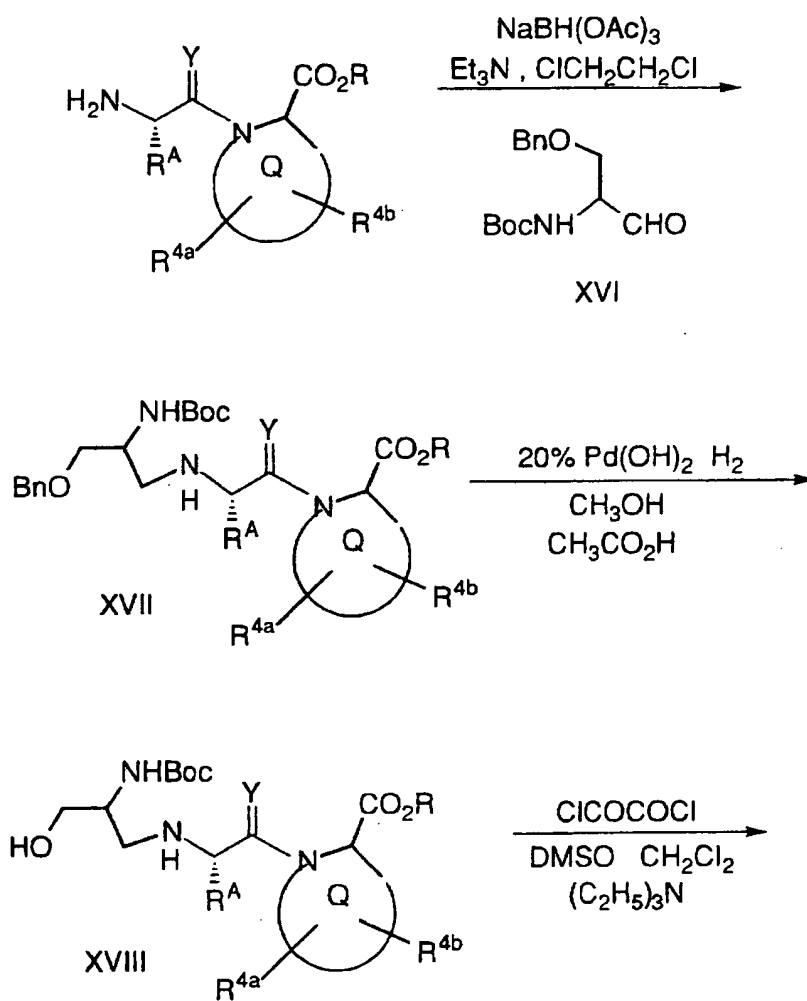
-191-

ALTERNATE REACTION SCHEME I FOR
COMPOUNDS (II-h) THROUGH (II-o)

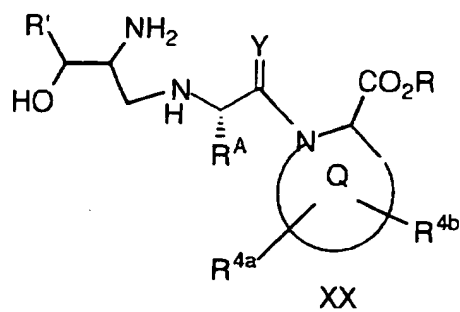
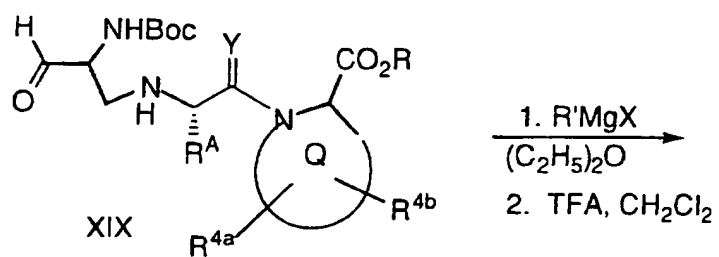


-192-

ALTERNATE REACTION SCHEME J FOR
COMPOUNDS (II-h) THROUGH (II-o)

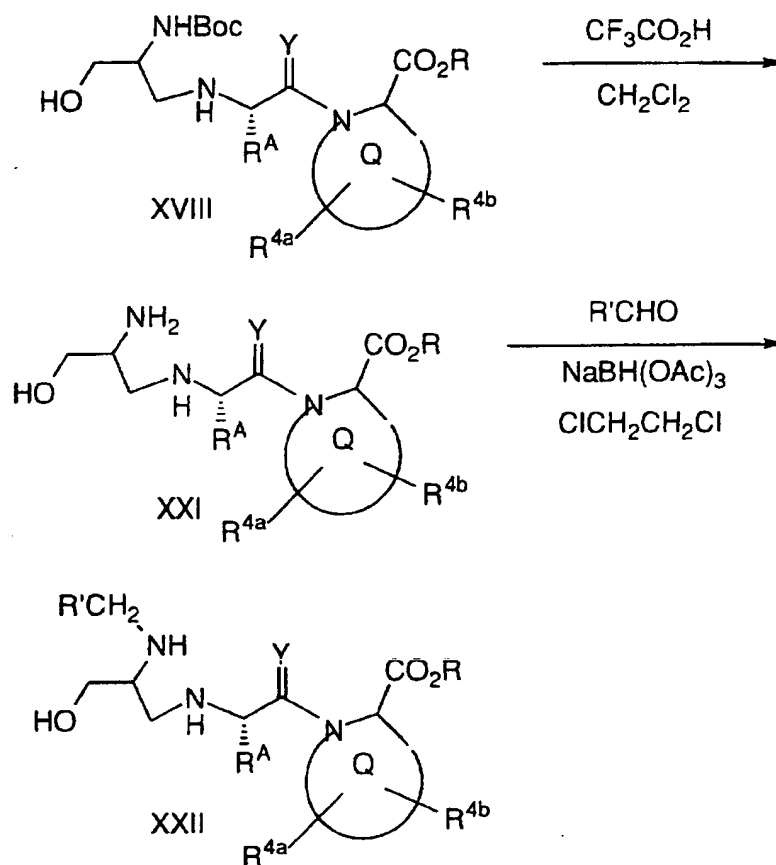


-193-

ALTERNATIVE REACTION SCHEME J (continued)

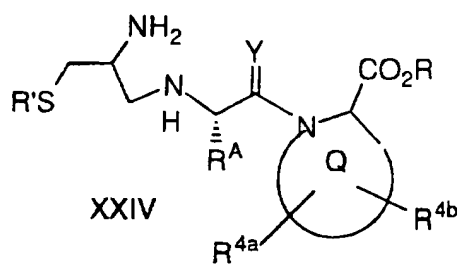
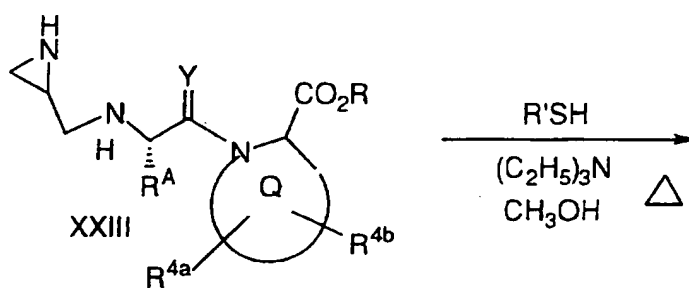
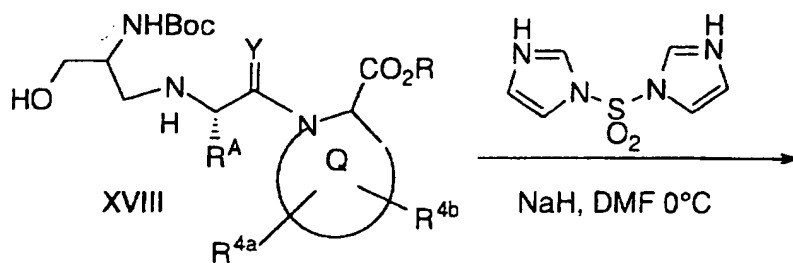
-194-

ALTERNATE REACTION SCHEME K FOR
COMPOUNDS (II-h) THROUGH (II-o)



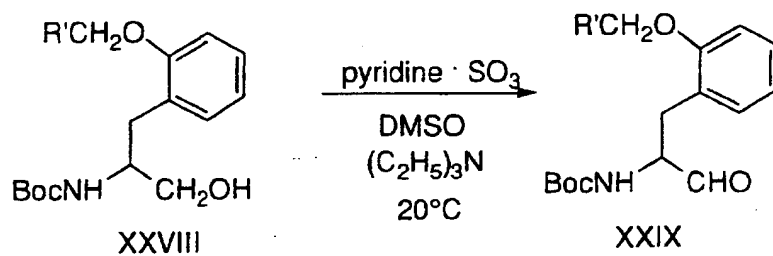
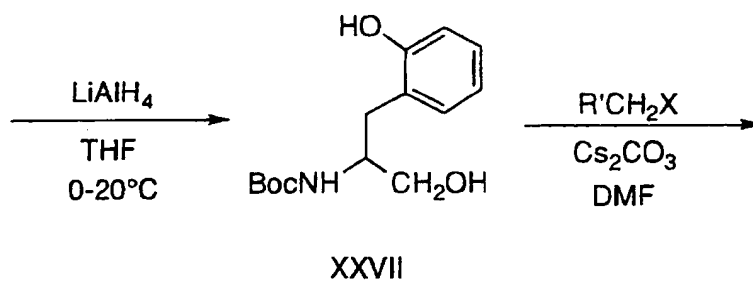
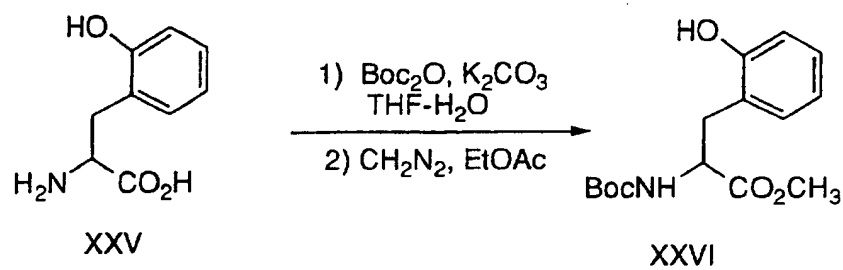
-195-

ALTERNATE REACTION SCHEME L FOR
COMPOUNDS (II-h) THROUGH (II-o)

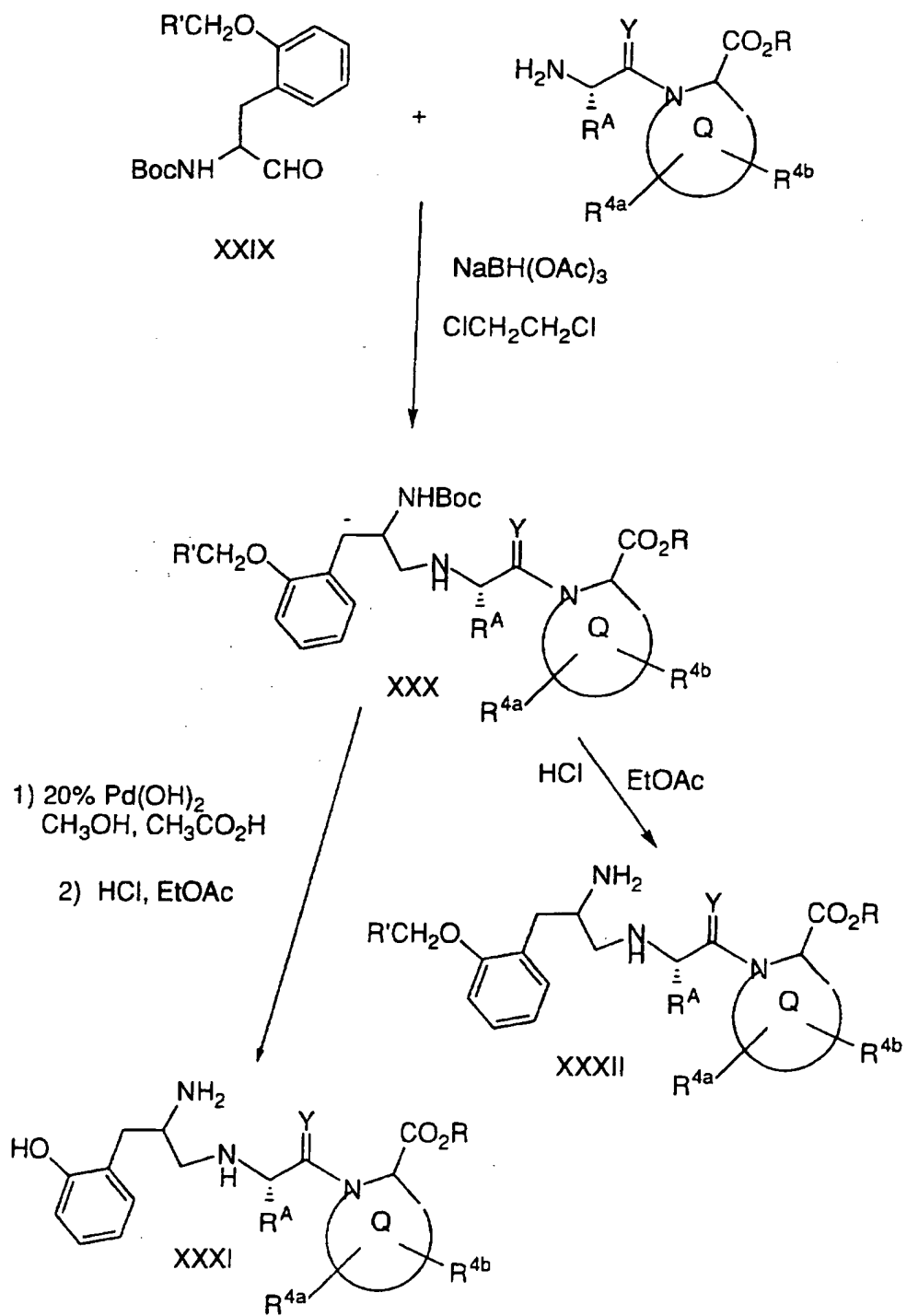


-196-

ALTERNATE REACTION SCHEME M FOR
COMPOUNDS (II-h) THROUGH (II-o)



-197-

ALTERNATE REACTION SCHEME M (CONT.)

-198-

Certain compounds used in the invention are described below.

EXAMPLE 1

5

(S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-imidazolymethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone dihydrochloride

10 Step A: 1-triphenylmethyl-4-(hydroxymethyl)-imidazole
To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction
15 mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

20 Step B: 1-triphenylmethyl-4-(acetoxymethyl)-imidazole
Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2
25 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. NaHCO₃, and brine, then dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder which was sufficiently pure for use in the next reaction.

30

Step C: 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the product from Step B (85.8 g, 225 mmol) and α -bromo-*p*-tolunitrile (50.1 g, 232 mmol) in 500 mL of EtOAc was
35 stirred at 60°C for 20 hours, during which a pale yellow precipitate

-199-

formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60°C for two hours, cooled to room temperature, and filtered again. The filtrate was
5 concentrated *in vacuo* to a volume 100 mL, reheated at 60°C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60°C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid
10 which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

15 Step D: 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole

To a solution of the acetate from Step C (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0°C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with
20 water, sat. aq. NaHCO₃ and brine. The solution was then dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

25 Step E: 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde

To a solution of the alcohol from Step D (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO₃-pyridine complex (40.5 g, 254 mmol). After 45 minutes, the reaction was poured into 2.5 L of EtOAc,
30 washed with water (4 x 1 L) and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the aldehyde as a white powder which was sufficiently pure for use in the next step without further purification.

-200-

Step F: (S)-2-(tert-butoxycarbonylamino)-N-methoxy-N-methyl-4-(methylthio)butanamide

L-N-Boc-methionine (30.0 g, 0.120 mol), *N,O*-dimethylhydroxylamine hydrochloride (14.1 g, 0.144 mol), EDC hydrochloride (27.7 g, 0.144 mol) and HOBT (19.5 g, 0.144 mol) were stirred in dry DMF (300 mL) at 20°C under nitrogen. More *N,O*-dimethylhydroxylamine hydrochloride (2.3 g, 23 mmol) was added to obtain pH 7-8. The reaction was stirred overnight, the DMF distilled to half the original volume under high vacuum, and the residue partitioned between ethyl acetate and sat. NaHCO₃ soln. The organic phase was washed with saturated sodium bicarbonate, water, 10% citric acid, and brine, and dried with sodium sulfate. The solvent was removed *in vacuo* to give the title compound.

Step G: (S)-2-(tert-butoxycarbonylamino)-4-(methylthio)butanal

A suspension of lithium aluminum hydride (5.02 g, 0.132 mol) in ether (500 mL) was stirred at room temperature for one hour. The solution was cooled to -50°C under nitrogen, and a solution of the product from Step F (39.8 g, ca. 0.120 mol) in ether (200 mL) was added over 30 min, maintaining the temperature below -40°C. When the addition was complete, the reaction was warmed to 5°C, then recooled to -45°C. Analysis by tlc revealed incomplete reaction. The solution was rewarmed to 5°C, stirred for 30 minutes, then cooled to -50°C. A solution of potassium hydrogen sulfate (72 g, 0.529 mol) in 200 mL water was slowly added, maintaining the temperature below -20°C. The mixture was warmed to 5°C, filtered through Celite, and concentrated *in vacuo* to provide the title aldehyde.

Step H: (S)-2-(tert-butoxycarbonylamino)-N-(3-chlorophenyl)-4-(methylthio)butanamine

To a solution of 3-chloroaniline (10.3 mL, 97.4 mmol), the product from Step G (23.9 g, 97.4 mmol), and acetic acid (27.8 mL, 487 mmol) in dichloroethane (250 mL) under nitrogen was added sodium triacetoxyborohydride (41.3 g, 195 mmol). The reaction was

-201-

stirred overnight, then quenched with saturated sodium bicarbonate solution. The solution was diluted with CHCl_3 , and the organic phase was washed with water, 10% citric acid and brine. The solution was dried over sodium sulfate and concentrated *in vacuo* to provide the
5 crude product (34.8 g) which was chromatographed on silica gel with 20% ethyl acetate in hexane to obtain the title compound.

Step I: (S)-4-(tert-butoxycarbonyl)-1-(3-chlorophenyl)-5-[2-(methylthio)ethyl]piperazin-2-one

10 A solution of the product from Step H (22.0 g, 63.8 mmol) in ethyl acetate (150 mL) was vigorously stirred at 0°C with saturated sodium bicarbonate (150 mL). Chloroacetyl chloride (5.6 mL, 70.2 mmol) was added dropwise, and the reaction stirred at 0°C for 2h. The layers were separated, and the ethyl acetate phase was washed
15 with 10% citric acid and saturated brine, and dried over sodium sulfate. After concentration *in vacuo*, the resulting crude product (27.6 g) was dissolved in DMF (300 mL) and cooled to 0°C under argon. Cesium carbonate (63.9 g, 196 mmol) was added, and the reaction was stirred for two days, allowing it to warm to room temperature. Another
20 portion of cesium carbonate (10 g, 30 mmol) was added, and the reaction was stirred for 16 hours. The DMF was distilled *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic phase was washed with saturated brine, and dried over sodium sulfate. The crude product was chromatographed on silica gel with 20-25%
25 ethyl acetate in hexane to obtain the title compound.

Step J: (S)-4-(tert-butoxycarbonyl)-1-(3-chlorophenyl)-5-[2-(methanesulfonyl)ethyl]piperazin-2-one

30 A solution of the product from Step I (14.2 g, 37 mmol) in methanol (300 mL) was cooled to 0 °C, and a solution of magnesium monoperoxyphthalate (54.9 g, 111 mmol) in 210 mL MeOH was added over 20 minutes. The ice bath was removed, and the solution was allowed to warm to room temperature. After 45 minutes, the reaction was concentrated *in vacuo* to half the original volume, then quenched by

-202-

the addition of 2N Na₂S₂O₃ soln. The solution was poured into EtOAc and sat NaHCO₃ solution, and the organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude sulfone. This material was chromatographed on silica gel with
5 60-100% ethyl acetate in hexane to obtain the titled compound.

Step K: (S)-1-(3-chlorophenyl)-5-[2-(methanesulfonyl)ethyl]piperazin-2-one

Through a solution of Boc-protected piperazinone from
10 Step J (1.39 g, 3.33 mmol) in 30 mL of EtOAc at 0 °C was bubbled anhydrous HCl gas. The saturated solution was stirred for 35 minutes, then concentrated *in vacuo* to provide the hydrochloride salt as a white powder. This material was suspended in EtOAc and treated with dilute aqueous NaHCO₃ solution. The aqueous phase was extracted with
15 EtOAc, and the combined organic mixture was washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting amine was reconcentrated from toluene to provide the titled material suitable for use in the next step.

20 Step L: (S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone dihydrochloride

To a solution of the amine from Step K (898 mg, 2.83 mmol) and imidazole carboxaldehyde from Step E (897 mg, 4.25 mmol)
25 in 15 mL of 1,2-dichloroethane was added sodium triacetoxyborohydride (1.21 g, 5.7 mmol). The reaction was stirred for 23 hours, then quenched at 0 °C with sat. NaHCO₃ solution. The solution was poured into CHCl₃, and the aqueous layer was back-extracted with CHCl₃. The combined organics were washed with brine, dried
30 (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel chromatography (95:5:0.5-90:10:0 EtOAc:MeOH:NH₄Cl), and the resultant product was taken up in EtOAc/methanol and treated with 2.1 equivalents of 1 M HCl/ether

-203-

solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

EXAMPLE 2

5

1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolyl-methyl]-2-piperazinone dihydrochloride

Step A: N-(3-chlorophenyl)ethylenediamine hydrochloride
10 To a solution of 3-chloroaniline (30.0 mL, 284 mmol) in 500 mL of dichloromethane at 0°C was added dropwise a solution of 4 N HCl in 1,4-dioxane (80 mL, 320 mmol HCl). The solution was warmed to room temperature, then concentrated to dryness *in vacuo* to provide a white powder. A mixture of this powder
15 with 2-oxazolidinone (24.6 g, 282 mmol) was heated under nitrogen atmosphere at 160°C for 10 hours, during which the solids melted, and gas evolution was observed. The reaction was allowed to cool, forming the crude diamine hydrochloride salt as a pale brown solid.

20 **Step B:** N-(tert-butoxycarbonyl)-N'-(3-chlorophenyl)ethylenediamine

The amine hydrochloride from Step A (*ca.* 282 mmol, crude material prepared above) was taken up in 500 mL of THF and 500 mL of sat. aq. NaHCO₃ soln., cooled to 0°C, and di-*tert*-
25 butylpyrocarbonate (61.6 g, 282 mmol) was added. After 30 h, the reaction was poured into EtOAc, washed with water and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the titled carbamate as a brown oil which was used in the next step without further purification.

30

Step C: N-[2-(tert-butoxycarbonyl)ethyl]-N-(3-chlorophenyl)-2-chloroacetamide

-204-

A solution of the product from Step B (77 g, *ca.* 282 mmol) and triethylamine (67 mL, 480 mmol) in 500 mL of CH₂Cl₂ was cooled to 0°C. Chloroacetyl chloride (25.5 mL, 320 mmol) was added dropwise, and the reaction was maintained at 0°C with stirring. After 3 h, another portion of chloroacetyl chloride (3.0 mL) was added dropwise. After 30 min, the reaction was poured into EtOAc (2 L) and washed with water, sat. aq. NH₄Cl soln, sat. aq. NaHCO₃ soln., and brine. The solution was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the chloroacetamide as a brown oil which was used in the next step without further purification.

Step D: 4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-2-piperazinone

To a solution of the chloroacetamide from Step C (*ca.* 282 mmol) in 700 mL of dry DMF was added K₂CO₃ (88 g, 0.64 mol). The solution was heated in an oil bath at 70-75°C for 20 hours, cooled to room temperature, and concentrated *in vacuo* to remove *ca.* 500 mL of DMF. The remaining material was poured into 33% EtOAc/hexane, washed with water and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the product as a brown oil. This material was purified by silica gel chromatography (25-50% EtOAc/hexane) to yield pure product, along with a sample of product (*ca.* 65% pure by HPLC) containing a less polar impurity.

Step E: 1-(3-chlorophenyl)-2-piperazinone

Through a solution of Boc-protected piperazinone from Step D (17.19 g, 55.4 mmol) in 500 mL of EtOAc at -78°C was bubbled anhydrous HCl gas. The saturated solution was warmed to 0°C, and stirred for 12 hours. Nitrogen gas was bubbled through the reaction to remove excess HCl, and the mixture was warmed to room temperature. The solution was concentrated *in vacuo* to provide the hydrochloride as a white powder. This material was taken up in 300 mL of CH₂Cl₂ and treated with dilute aqueous NaHCO₃ solution. The aqueous phase was extracted with CH₂Cl₂ (8 x 300 mL) until tlc analysis indicated

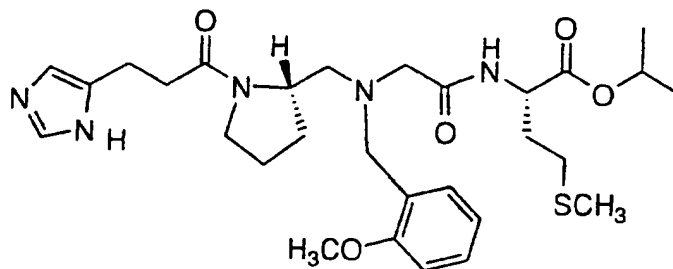
-205-

complete extraction. The combined organic mixture was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the titled free amine as a pale brown oil.

5 Step F: 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-
2-piperazinone dihydrochloride

To a solution of the amine from Step E (55.4 mmol, prepared above) in 200 mL of 1,2-dichloroethane at 0°C was added 4Å powdered molecular sieves (10 g), followed by sodium triacetoxyborohydride (17.7 g, 83.3 mmol). The imidazole carboxaldehyde from Step E of Example 1 (11.9 g, 56.4 mmol) was added, and the reaction was stirred at 0°C. After 26 hours, the reaction was poured into EtOAc, washed with dilute aq. NaHCO₃, and the aqueous layer was back-extracted with EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting product was taken up in 500 mL of 5:1 benzene:CH₂Cl₂, and propylamine (20 mL) was added. The mixture was stirred for 12 hours, then concentrated *in vacuo* to afford a pale yellow foam. This material was purified by silica gel chromatography (2-7% MeOH/CH₂Cl₂), and the resultant white foam was taken up in CH₂Cl₂ and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

EXAMPLE 3



25 N-[1-(1H-imidazol-4-propionyl)pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester

-206-

Step A: 2-Methoxybenzylglycine methyl ester

2-Methoxybenzyl alcohol (53.5 g, 0.39 mol) was dissolved in CH₂Cl₂ (200 mL), treated with diisopropylethylamine (81 mL, 0.74 mol), cooled to 0°C. with stirring in an ice-CH₃OH bath under Ar, and treated dropwise with methanesulfonyl chloride (33 mL, 0.43 mol). After 0.5 hr, the reaction mixture was left to warm to ambient temperature and stirred for 4 hr. This solution and diisopropylethylamine (202.5 mL, 1.16 mol) were added alternately portionwise with to a slurry of glycine methyl ester hydrochloride (146.5 g, 1.17 mol) in DMF (250 mL) with stirring at 0°C. The reaction mixture was left to stir and warm to room temperature overnight. The DMF was removed under reduced pressure, and the residue was partitioned between EtOAc (1 L) and satd NaHCO₃ solution (1 L). The aqueous layer was washed with EtOAc (2 x 600 mL), the organics combined, washed with brine and dried (MgSO₄). Filtration and concentration to dryness gave the title compound after chromatography (SiO₂, 1-5% CH₃OH/CH₂Cl₂).

Step B: N-[(2S)-(t-Butoxycarbonylpyrrolidinyl-methyl)-N-(2-methoxybenzyl)glycine methyl ester

2-Methoxybenzylglycine methyl ester (27.4 g, 0.131 mol) was dissolved in 1,2-dichloroethane (500 ml), 3 Å molecular sieves (20 g) were added, and the pH of the reaction mixture adjusted to pH 5 with acetic acid (7.5 mL, 0.131 mol). N-(t-Butoxycarbonyl)-L-proline (26.1 g, 0.131 mol) (J. Org. Chem. (1994) **59**, [21], 6287-95) was added followed by sodium triacetoxyborohydride (33.2 g, 0.157 mol). The mixture was stirred at ambient temperature for 18 h, filtered through celite and concentrated. The residue was partitioned between EtOAc and sat. NaHCO₃ (500 ml/100 ml). The aqueous layer was washed with EtOAc (3x100 ml). The organic layers were combined, dried with Na₂SO₄, filtered, and concentrated to give the title compound.

-207-

Step C: N-[(2S)-(t-Butoxycarbonylpyrrolidinyl-methyl)-N-(2-methoxybenzyl)glycine

N-[(2S)-(t-Butoxycarbonylpyrrolidinylmethyl)-N-(2-methoxybenzyl)glycine methyl ester (7.0 g, 0.018 mol) was dissolved in
5 CH₃OH (150 ml) and 1N NaOH (71 ml, 0.071 mol) was added with cooling in an ice-water bath. The mixture was stirred at ambient temperature for 2 hr, neutralized with 1N HCl (71 ml, 0.071 mol), concentrated to remove the CH₃OH, and the residue extracted with EtOAc (3x200 mL). The organic layers were combined, dried with
10 Mg₂SO₄, filtered, and concentrated to give the title compound as a foam.

Step D: Methionine isopropyl ester hydrochloride

N-(t-Butoxycarbonyl)methionine (25 g, 0.1 mol), isopropyl
15 alcohol (11.8 mL, 0.15 mol), EDC (21.1 g, 0.11 mol), and 4-dimethylaminopyridine (DMAP) (1.22 g, 0.01 mol) were dissolved in CH₂Cl₂ (400 mL) with stirring in an ice-water bath. After 2 h the bath was removed, and the solution was left to stir o.n. at RT. The reaction mixture was concentrated to dryness, then partitioned between EtOAc
20 and H₂O, the aqueous layer washed with EtOAc (2 x 50 mL), the organics combined, washed with NaHCO₃ soln, brine, and dried (Na₂SO₄). Filtration and concentration to dryness gave a yellow oil after chromatography (flash silica gel column, hexane: EtOAc, 6:1 to 5:1).

25 N-(t-Butoxycarbonyl)methionine isopropyl ester (20.5 g, 0.07 mol) was dissolved in EtOAc (200 mL) with stirring and cooling to -20°C in a dry ice- acetone bath. HCl gas was bubbled into the solution for 10 min, the flask was stoppered and stirred for 1 h. Tlc (EtOAc: hexane, 1:3) indicates loss of starting material. Argon was bubbled
30 through the soln for 5 min, then it was concentrated to dryness to give the title compound as a white solid.

-208-

Step E: N-[(2S)-(t-Butoxycarbonylpyrrolidinyl-methyl)-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester
N-[(2S)-(t-Butoxycarbonylpyrrolidinylmethyl)-N-(2-methoxybenzyl)glycine (from step C) (5.98 g, 0.0158 mol), dissolved
5 in CH₂Cl₂ (100 mL), was treated with HOBT (2.57 g, 0.019 mol), EDC (4.54 g, 0.024 mol), and methionine isopropyl ester hydrochloride (4.33 g, 0.019 mol). The pH was adjusted to 7.5 with Et₃N (8.81 mL, 0.063 mol) and the mixture was stirred at ambient temperature for 18 h. The mixture was diluted with EtOAc (150 mL) and washed sequentially with
10 10% citric acid soln, saturated NaHCO₃ solution, brine, and dried (MgSO₄). Filtration and concentration to dryness gave the title compound as a thick oil. This was used without further purification.

Step F: N-((2S)-Pyrrolidinylmethyl)-N-(2-methoxybenzyl)-glycyl-methionine isopropyl ester bis hydrochloride
15 N-[(2S)-(t-Butoxycarbonylpyrrolidinylmethyl)-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester (0.85 g, 1.54 mmol) was dissolved in EtOAc (25 mL) and cooled to 0°C. HCl was bubbled through the mixture until the soln was saturated, and it was stoppered
20 and stirred for 3 hr. Argon was bubbled through the mixture to remove excess HCl and the mixture was then concentrated to give the title compound.

Step G: N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine
25 isopropyl ester
N-((2S)-Pyrrolidinylmethyl)-N-(2-methoxybenzyl)glycyl methionine isopropyl ester bis hydrochloride (0.800 g, 1.53 mmol), dissolved in DMF (30 mL), was treated with 1H-imidazol-4-propionic
30 acid (0.43 g, 3.05 mmol) (prepared by catalytic hydrogenation of urocanic acid in 20% acetic acid with Pd on carbon), and BOP reagent (1.35 g, 3.05 mmol). The pH was adjusted to 7.5 with N-methyl-morpholine (0.756 mL, 6.89 mmol), and the mixture was stirred

-209-

at ambient temperature for 18 h. The mixture was concentrated to dryness, diluted with EtOAc (100 mL), washed with 5% Na₂CO₃ solution, brine, and dried (MgSO₄). Filtration and concentration to dryness gave an oil which was purified by chromatography (silica gel, 95:5 CH₂Cl₂/MeOH) to give the title compound as a foam.

¹H NMR (CD₃OD); δ 7.58 (d, 1H, J=1 Hz), 7.25-7.31 (m, 2H), 6.89-7.00 (m, 2H), 6.81 (s, 1H), 5.00-5.06 (m, 1H), 4.49-4.56 (m, 1H), 4.23-4.30 (m, 1H), 3.91 (d, 1H, J=13 Hz), 3.86 (s, 3H), 3.54 (d, 1H, J=13 Hz), 3.30-3.41 (m, 2H), 3.36 (d, 1H, J=17 Hz), 3.15 (d, 1H, J=17 Hz), 2.85-2.92 (m, 2H), 2.56-2.77 (m, 3H), 2.30-2.45 (m, 3H), 2.05-2.17 (m, 1H), 2.04 (s, 3H), 1.69-1.86 (m, 5H), 1.24 (d, 6H, J=6 Hz).

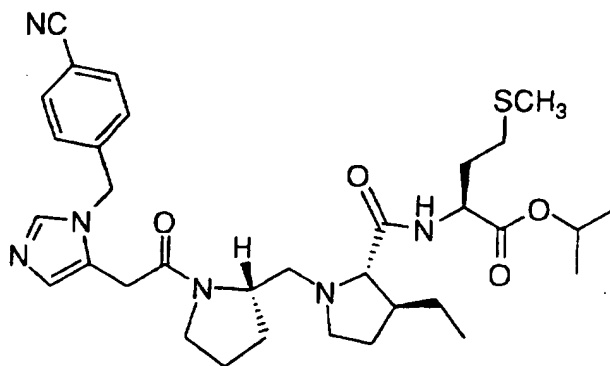
Anal. calculated for C₂₉H₄₃N₅O₅S • 0.6 H₂O:

C, 59.59; H, 7.62; N, 11.98;

Found: C, 59.58; H, 7.43; N, 12.02.

EXAMPLE 4

(N-[1-Cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-
3(S)-ethyl-prolyl methionine isopropyl ester



Step A: Diethyl 1-Acetyl-5-hydroxy-3-ethylpyrrolidine-2,2-dicarboxylate

Sodium (4.02 g, 0.175 mol) was dissolved in a stirred solution of diethyl acetamidomalonate (235.4 g, 1.19 mol) in abs EtOH

-210-

(1.4 L) at ambient temperature under argon. The reaction mixture was cooled to 0°C, and trans-2-pentenal (100 g, 1.08 mol) was added dropwise maintaining the reaction temperature at <5°C. After the addition, the reaction was allowed to warm to room temperature, stirred for 4 h, then quenched with acetic acid (28 mL). The solution was concentrated *in vacuo*, and the residue dissolved in EtOAc (1.5 L), washed with 10% NaHCO₃ solution (2 x 300 mL), brine, and dried (MgSO₄). The solution was filtered and concentrated to 700 mL, then heated to reflux and treated with hexane (1 L). On cooling, the title compound precipitated and was collected, mp 106 - 109°C. ¹H NMR (CD₃OD) δ 5.65 (d, 1H, J = 5 Hz), 4.1 - 4.25 (m, 4H), 2.7-2.8 (m, 1H), 2.21 (s, 3H), 2.10 (dd, 1H, J = 6, 13, Hz), 1.86- 1.97 (m, 2H), 1.27 (t, 3H, J = 7 Hz), 1.23 (t, 3H, J = 7 Hz), 1.1- 1.25 (m, 1H), 0.97 (t, 3H, J = 7 Hz).

15 Step B: Diethyl 1-Acetyl-3-ethylpyrrolidine-2,2-dicarboxylate

To a solution of diethyl 1-acetyl-5-hydroxy-3-ethylpyrrolidine-2,2-dicarboxylate (287 g, 0.95 mol) and triethylsilane (228 mL, 1.43 mol) in CH₂Cl₂ (3 L) under argon was added trifluoroacetic acid (735 mL, 9.53 mol) dropwise with stirring while maintaining the internal temperature at 25 °C by means of an ice bath. After stirring for 3 h at 23°C, the solution was concentrated *in vacuo*, the residue diluted with CH₂Cl₂ (1.5 L), then treated with H₂O (1 L) and solid Na₂CO₃ with vigorous stirring until the solution was basic. The organic layer was separated, dried (Na₂SO₄), filtered, then concentrated to give the title compound as a yellow oil which was used without further purification.

Step C: 3-Ethylproline hydrochloride (Cis:Trans Mixture)

Diethyl 1-acetyl-3-ethylpyrrolidine-2,2-dicarboxylate (373 g, 0.95 mol) was suspended in 6N HCl (2 L) and HOAc (500 mL) and heated at reflux for 20 h. The reaction mixture was cooled, washed with EtOAc (1L), then concentrated *in vacuo* to give an oil which crystallized upon trituration with ether to give the title compound.

-211-

^1H NMR (D_2O) δ 4.23 (d, 1H, $J = 8$ Hz), 3.84 (d, 1H, $J = 8$ Hz), 3.15-3.4 (m, 4H), 2.33-2.44 (m, 1H), 2.19-2.4 (m, 1H), 2.02-2.15 (m, 2H), 1.53-1.72 (m, 3H), 1.23-1.43 (m, 2H), 1.0-1.15 (m, 1H), 0.75-0.83 (m, 6H).

5

Step D: N-[(*tert*-Butyloxy)carbonyl]-*cis:trans*-3-ethylproline methyl ester

3-Ethylproline hydrochloride (Cis:Trans Mixture) (20 g, 0.11 mol) was dissolved in CH_3OH (200 mL), and the solution was saturated with HCl gas, then stirred at 23°C for 24 h. Argon was bubbled through the solution to remove excess HCl. The solution was treated with NaHCO_3 (>84 g) to a pH of 8, then di-*tert*-butyl dicarbonate (25.1 g, 0.115 mol) dissolved in CH_3OH (20 mL) was added slowly. After stirring for 18 h at 23°C , the mixture was filtered, the filtrate concentrated, and the residue triturated with EtOAc, filtered again, and concentrated to give the title compound as an oil.

20

Step E: N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline and N-[(*tert*-Butyloxy)carbonyl]-*cis*-3-ethylproline methyl ester

N-[(*tert*-Butyloxy)carbonyl]-*cis,trans*-3-ethylproline methyl ester (29.1 g, 0.113 mol) was dissolved in CH_3OH (114 mL) with cooling to 0°C , then treated with 1 N NaOH (114 mL). After stirring for 20 h at 23°C , the solution was concentrated to remove the CH_3OH and then extracted with EtOAc (3 x). The organic layers were combined, dried (MgSO_4), filtered, and concentrated to give 12.8 g of N-[(*tert*-Butyloxy)carbonyl]-*cis*-3-ethylproline methyl ester as an oil. The aqueous layer was acidified with solid citric acid and extracted with EtOAc (2 x), the organic layers combined, dried (MgSO_4), filtered, and concentrated to give N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline as an oil. ^1H NMR (CD_3OD) δ 3.86 and 3.78 (2 d, 1H, $J = 6$ Hz), 3.33-3.58 (m, 2H), 2.01-2.22 (m, 2H), 1.5-1.74 (m, 2H), 1.33-1.5 (m, 1H), 1.45 and 1.42 (2 s, 9H), 0.98 (t, 3H, $J = 8$ Hz).

-212-

Step F: 3(S)-Ethyl-2(S)-proline hydrochloride

N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline (15.5 g, 0.064 mol), S- α -methylbenzylamine (9.03 mL, 0.070 mol), HOBT (10.73 g, 0.070 mol), and N-methylmorpholine (8 mL, 0.076 mol) were dissolved in CH₂Cl₂ (150 mL) with stirring in an ice-H₂O bath, treated with EDC (13.4 g, 0.070 mol) stirred at 23°C for 48 h. The reaction mixture was partitioned between EtOAc and 10% citric acid solution, the organic layer washed with satd NaHCO₃ solution, brine and dried (MgSO₄), filtered, and concentrated to give an oil. This oil was dissolved in a minimum amount of ether (10 mL) to crystallize the desired S,S,S diastereomer (4.2 g), mp 118-121°C. A solution of this product in 8N HCl (87 mL) and glacial acetic acid (22 mL) was heated at reflux overnight. The solution was concentrated on a rotary evaporator, and the residue taken up in H₂O and extracted with ether. The aqueous layer was concentrated to dryness to give a 1:1 mixture of 3(S)-ethyl-2(S)-proline hydrochloride and α -methylbenzylamine.

3(S)-Ethyl-2(S)-proline containing α -methylbenzylamine (2.0 g, 0.0128 mol) was dissolved in dioxane (10 mL) and H₂O (10 mL) with stirring and cooling to 0°C. N,N-diisopropylethylamine (2.2 mL, 0.0128 mol) and di-*tert*-butyl-dicarbonate (2.79 g, 0.0128 mol) were added and stirring was continued at 23°C for 48 h. The reaction mixture was partitioned between EtOAc (60 mL) and H₂O (30 mL), the organic layer washed with 0.5N NaOH (2 x 40 mL), the aqueous layers combined and washed with EtOAc (30 mL) and this layer back-extracted with 0.5 N NaOH (30 mL). The aqueous layers were combined and carefully acidified at 0°C with 1N HCl to pH 3. This mixture was extracted with EtOAc (3 x 40 mL), the organics combined, dried (MgSO₄), filtered and concentrated to give N-[(*tert*-Butyloxy)carbonyl]-3(S)-ethyl-2(S)-proline as a colorless oil. N-[(*tert*-Butyloxy)carbonyl]-3(S)-ethyl-2(S)-proline was dissolved in EtOAc (50 mL) and the solution was saturated with HCl gas with cooling in an ice-H₂O bath. The solution was stoppered and stirred at 0°C. for 3 hr. Argon was

-213-

bubbled through the solution to remove excess HCl, and the solution was concentrated to dryness to give 3(S)-ethyl-2(S)-proline hydrochloride.

5 Step G: N-(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-proline

3(S)-Ethyl-2(S)-proline hydrochloride (2.33 g, 0.013 mol) was dissolved in CH₃OH (20 mL), treated with 3A molecular sieves (2 g) and KOAc (1.27 g, 0.013 mol) to adjust the pH of the reaction mixture to 4.5-5, then N-[(*tert*-Butyloxy)carbonyl-prolinal (Pettit et al., J. Org. Chem. (1994) **59**, [21] 6287-95) (3.36 g, 0.017 mol) was added, and the mixture was stirred for 16 hrs at room temperature. The reaction mixture was filtered, quenched with aq satd NaHCO₃ (5 mL) and concentrated to dryness. The residue was extracted with CHCl₃. The extract was dried (MgSO₄), filtered, and concentrated to give the title compound and inorganic salts.

Step H: N-(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester

20 N-(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-proline (2.4 g, 0.008 mol), methionine isopropyl ester hydrochloride (2.21 g, 0.0097 mol), HOBt (1.49 g, 0.0097 mol) and EDC (1.86 g, 0.0097 mol) were dissolved in DMF (15 mL) at room temperature and treated with N-methylmorpholine (3 mL, 0.024 mol).
25 The reaction mixture was stirred overnight at room temperature, then concentrated and partitioned between EtOAc and H₂O. The organic layer was washed with aq satd NaHCO₃ solution, brine, and dried (MgSO₄). The crude product was chromatographed on a flash silica gel column eluting with hexane: EtOAc, 7:3 to give N-(t-butyloxy-carbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine
30 isopropyl ester.

-214-

isopropyl ester hydrochloride

5 N-(t-butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester (1.38 g, 0.0028 mol) was dissolved in EtOAc (40 mL), cooled to -20°C, saturated with HCl gas, and stirred at 0°C. for 1.25 hr, and room temperature for 0.25 hr. Concentration to dryness gave pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester hydrochloride.

10 Step J: Preparation of 1H-Imidazole-4- acetic acid methyl ester hydrochloride

A solution of 1H-imidazole-4-acetic acid hydrochloride (4.00g, 24.6 mmol) in methanol (100 ml) was saturated with gaseous hydrogen chloride. The resulting solution was allowed to stand at room temperature (RT) for 18hr. The solvent was evaporated in vacuo to afford the title compound as a white solid.

15 ¹H NMR(CDCl₃, 400 MHz) δ 8.85(1H, s), 7.45(1H, s), 3.89(2H, s) and 3.75(3H, s) ppm.

20 Step K: Preparation of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester

To a solution of 1H-Imidazole-4- acetic acid methyl ester hydrochloride (24.85g, 0.141mol) in dimethyl formamide (DMF) (115ml) was added triethylamine (57.2 ml, 0.412mol) and triphenylmethyl bromide(55.3g, 0.171mol) and the suspension was stirred for 25 24hr. After this time, the reaction mixture was diluted with ethyl acetate (EtOAc) (1 l) and water (350 ml). The organic phase was washed with sat. aq. NaHCO₃ (350 ml), dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by flash chromatography (SiO₂, 0-100% ethyl acetate in hexanes; gradient elution) to provide the title compound as a white solid.

30 ¹H NMR (CDCl₃, 400 MHz) δ 7.35(1H, s), 7.31(9H, m), 7.22(6H, m), 6.76(1H, s), 3.68(3H, s) and 3.60(2H, s) ppm.

-215-

Step L: Preparation of [1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester

To a solution of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (8.00g, 20.9mmol) in acetonitrile (70 ml) was added bromo-p-toluenitrile (4.10g, 20.92 mmol) and heated at 55°C for 3 hr. After this time, the reaction was cooled to room temperature and the resulting imidazolium salt (white precipitate) was collected by filtration. The filtrate was heated at 55°C for 18hr. The reaction mixture was cooled to room temperature and evaporated in vacuo. To the residue was added EtOAc (70 ml) and the resulting white precipitate collected by filtration. The precipitated imidazolium salts were combined, suspended in methanol (100 ml) and heated to reflux for 30min. After this time, the solvent was removed in vacuo, the resulting residue was suspended in EtOAc (75ml) and the solid isolated by filtration and washed (EtOAc). The solid was treated with sat aq NaHCO₃ (300ml) and CH₂Cl₂ (300ml) and stirred at room temperature for 2 hr. The organic layer was separated, dried (MgSO₄) and evaporated in vacuo to afford the title compound as a white solid : ¹H NMR(CDCl₃, 400 MHz) δ 7.65(1H, d, J=8Hz), 7.53(1H, s), 7.15(1H, d, J=8Hz), 7.04(1H, s), 5.24(2H, s), 3.62(3H, s) and 3.45(2H, s) ppm.

Step M: Preparation of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid

A solution of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester (4.44g, 17.4mmol) in THF (100ml) and 1 M lithium hydroxide (17.4 ml, 17.4 mmol) was stirred at RT for 18 hr. 1 M HCl (17.4 ml) was added and the THF was removed by evaporation in vacuo. The aqueous solution was lyophilized to afford the title compound containing lithium chloride as a white solid. ¹H NMR(CD₃OD, 400 MHz) δ 8.22(1H, s), 7.74(1H, d, J=8.4Hz), 7.36(1H, d, J=8.4Hz), 7.15(1H, s), 5.43(2H, s) and 3.49(2H, s) ppm.

-216-

Step N: Preparation of N-[(1-(4-Cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester

- [1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid • LiCl
5 (0.416 g, 1.47 mmol), pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester hydrochloride (Step I) (0.63 g, 1.33 mmol), HOObt (0.239 g, 1.47 mmol), and EDC (0.281 g, 1.47 mmol) were dissolved in degassed DMF (20 mL) with stirring at room temperature, N-methylmorpholine (0.8 mL, 5.32 mmol) was added to achieve a pH
10 of 7, and stirring was continued overnight. The reaction mixture was concentrated to remove most of the DMF, and the residue was partitioned between EtOAc and aq satd NaHCO₃ solution. The aq layer was washed with EtOAc, the organics combined, washed with brine and dried (MgSO₄). Filtration and concentration to dryness gave the title
15 compound after chromatography on silica gel eluting with CH₂Cl₂:CH₃OH, 95:5.

Anal. calcd for C₃₃H₄₆N₆O₄S • 0.7 H₂O:

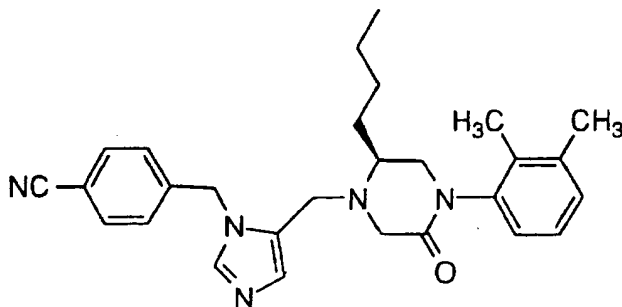
C, 62.38; H, 7.52; N, 13.23;

Found: C, 62.40; H, 7.17; N, 13.11.

20 FAB MS 623 (M+1)

EXAMPLE 5

25 2(S)-n-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one



-217-

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-
2(S)-(2-methoxyethyl)piperazin-5-one ditrifluoroacetic acid salt

Step A: N-Methoxy-N-methyl 4-benzyloxy-2(S)-(tert-
butoxycarbonylamino)butanamide

5
4-Benzyloxy-2(S)-(tert-butoxycarbonylamino)butanoic acid
(1.00 g, 3.23 mmol) was converted to the title compound following the
procedure described in Example 24, Step A, using EDC · HCl (0.680 g,
3.55 mmol). HOBt (0.436 g, 3.23 mmol) and N,O-dimethylhydroxyl-
10 amine hydrochloride (0.473 g, 4.85 mmol) in DMF (50 mL) at pH 7.
After workup, the title compound was obtained as a clear gum.

Step B: 4-(1-Benzyloxyethyl)-2(S)-(tert-butoxycarbonylamino)
butanal

15 The title compound was obtained by lithium aluminum
hydride reduction of the product of Step A using the procedure
described in Example 24, Step B.

Step C: N-(2,3-Dimethylphenyl)-4-(2-benzyloxyethyl)-2-(S)-(tert-
butoxycarbonylamino)butanamine

20 The title compound was prepared from the product of Step
C according to the procedure described in Example 24, Step C, using
2,3-dimethylaniline (0.505 mL, 4.14 mmol), sodium triacetoxyboro-
hydride (1.20 g, 5.65 mmol) and crushed molecular sieves (1 g) at pH
25 5 in dichloroethane (20 mL). The title compound was obtained after
purification on silica gel, eluting with 15% ethyl acetate in hexane.

Step D: 2(S)-(2-Benzyloxyethyl)-1-tert-butoxycarbonyl-4-(2,3-
dimethylphenyl)piperazin-5-one

30 The title compound was prepared from the product of Step
C according to the procedure described in Example 24, Step D, using
chloroacetyl chloride (0.21 mL, 2.57 mmol) in 60 mL 1:1 ethyl acetate:
saturated sodium bicarbonate, followed by reaction of the crude product
with sodium hydride (0.373 g, 60% dispersion in oil, 9.32 mmol) in

-218-

DMF (30 mL). After workup, the crude product was chromatographed on silica gel with 30% ethyl acetate in hexane to obtain the title compound.

5 Step E: 1-tert-Butoxycarbonyl-4-(2,3-dimethylphenyl)-2(S)-(2-hydroxyethyl)piperazin-5-one

 The product from Step D was dissolved in methanol (40 mL) and 10% Pd/C was added (0.160 g). The reaction was shaken under 60 psi hydrogen overnight. The catalyst was removed by
10 filtration, and the solvent evaporated to give the title compound.

Step F: 1-tert-Butoxycarbonyl-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one

 The product from Step E (0.241 g, 0.688 mmol) was
15 dissolved in DMF (10 mL) containing methyl iodide (0.21 mL, 3.44 mmol) and the stirred solution cooled to 0°C under nitrogen. Sodium hydride (0.070 g, 60% dispersion in oil, 1.72 mmol) was added and the reaction stirred for 1h. The reaction was quenched with water, and the DMF removed under vacuum. The residue was partitioned between
20 ethyl acetate and water, and the organic phase washed with saturated brine and dried over magnesium sulfate. The crude product was chromatographed on silica gel with 40% ethyl acetate in hexane to give the title compound.

25 Step G: 4-(2,3-Dimethylphenyl)-2(S)-(2-methoxyethyl)-1-[4-(1-triphenylmethylimidazolyl)methyl]piperazin-5-one

 The product from Step F (0.113 g, 0.312 mmol) was converted to the title compound according to the procedure described in Example 24, Step E, except using 30% trifluoroacetic acid in dichloromethane (10 mL) for 1 h for the initial deprotection. The
30 volatiles were removed *in vacuo*, and the residue dissolved in dichloroethane. Triethylamine was added to obtain pH 5. Sodium triacetoxyborohydride (0.100 g, 0.468 mmol) and 1-triphenylmethyl-

-219-

4-imidazolylcarboxaldehyde (0.1164 g, 0.343 mmol) was added. The reaction was stirred overnight at 20°C then poured into saturated sodium bicarbonate solution. The organic phase was washed with saturated brine and dried over magnesium sulfate. Silica gel chromatography using 5% methanol in chloroform as eluant yielded the title compound.

Step H: 1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one ditrifluoroacetic acid salt

The product from Step G (0.182 g, 0.312 mmol) was converted to the title compound according to the procedure described in Example 25, using 4-cyanobenzylbromide (0.061 g, 0.312 mmol) in acetonitrile (10 mL), followed by reaction of the crude imidazolium salt with triethylsilane (0.13 mL) and trifluoroacetic acid (2 mL) in dichloromethane (6 mL). Purification was accomplished by reverse phase preparative HPLC with a mixed gradient of 0%-70% acetonitrile/0.1% TFA; 100%-30% 0.1% aqueous TFA over 60 min. The title compound was isolated after lyophilization from water. FAB ms (m+1) 458.

Anal. Calc. for $C_{27}H_{31}N_5O_2 \cdot 0.35 H_2O \cdot 2.0 TFA$:

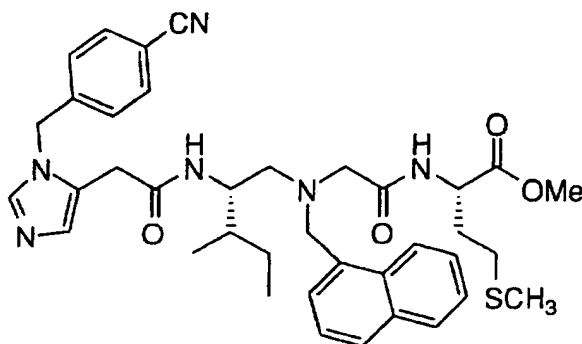
C, 53.81; H, 4.91; N, 10.21.

Found: C, 53.83; H, 4.95; N, 10.29.

EXAMPLE 6

N-[2(S)-N'-(1-(4-Cyanophenyl-methyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester

-220-



Preparation of N-[2(S)-N'-(1-(4-Cyanophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine bis trifluoroacetate

5

Step A: Preparation of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (**23**)

To a suspension of 1H-imidazole-4-acetic acid methyl ester hydrochloride (**1**, 7.48, 42.4 mmol) in methylene chloride (200 ml) was added triethylamine (17.7 ml, 127 mmol) and triphenylmethyl bromide (16.4 g, 50.8 mmol) and stirred for 72 h. After this time, reaction mixture was washed with sat. aq. sodium bicarbonate (100 ml) and water (100 ml). The organic layer was evaporated *in vacuo* and purified by flash chromatography (30-100% ethyl acetate/hexanes gradient elution) to provide **23** as a white solid.

15

¹H NMR (CDCl₃, 400 MHz) δ 7.35 (1H, s), 7.31 (9H, m), 7.22 (6H, m), 6.76 (1H, s), 3.68 (3H, s) and 3.60 (2H, s) ppm.

20

Step B: Preparation of 1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid methyl ester (**16**)

To a solution of 1-(triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (**23**, 274 mg, 0.736 mmol) in acetonitrile (10 ml) was added 4-nitrobenzylbromide (159 mg, 0.736 mmol) and heated to 55°C for 16 h. After this time, the reaction was cooled to room temperature, treated with ethyl acetate (20 ml) and the resulting precipitate was filtered. The filtrate was concentrated to dryness *in vacuo* and the residue was redissolved in acetonitrile (4 ml) and heated to 65°C for

25

-221-

3 h. After this time, the reaction mixture was evaporated to dryness and combined with initial precipitate. This residue was dissolved in methanol (5 ml) and heated to reflux for 30 min. The resulting solution was evaporated in vacuo and the residue was purified by flash chromatography (2-5% methanol/methylene chloride gradient elution) to provide **16**.

¹H NMR (CDCl₃, 400 MHz) δ 8.20 (2H, d, J=8.8 Hz), 7.53 (1H, s), 7.19 (2H, d, J=8.8 Hz), 7.03 (1H, s), 5.28 (2H, s), 3.61 (3H, s) and 3.44 (2H, s) ppm.

10

Step C: 1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid hydrochloride

1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid methyl ester (0.115 g, 0.42 mmol) was dissolved in 1.0N hydrochloric acid (10 ml) and heated at -55°C for 3 h. The solution was evaporated *in vacuo* to give the compound as a white solid.

¹H NMR (CD₃OD, 400 MHz) δ 9.06 (1H, s), 8.27 (2H, d, J=8.8 Hz), 7.61 (1H, s), 7.55 (2H, d, J=8.8 Hz), 5.63 (2H, s) and 3.81 (2H, s) ppm.

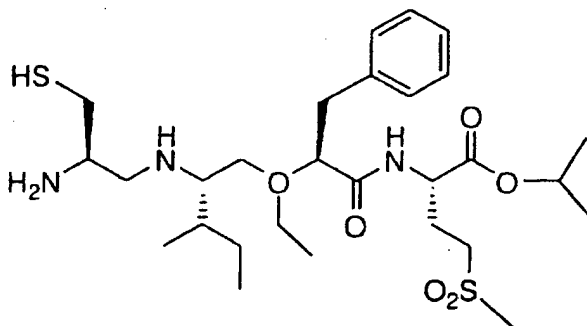
20 Step D: N-[2(S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis trifluoroacetate

To a solution of 1-(4-nitrophenylmethyl)-1H-imidazol-5-ylacetic acid hydrochloride, N-[2(S)-amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis hydrochloride (209 mg, 0.392 mmol) and 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOGBT, 64 mg, 0.39 mmol) in methylene chloride (10 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 75.2 mg, 0.392 mmol) and triethylamine (219 µl, 1.57 mmol) and the mixture stirred overnight at room temperature. After this time, satd. aq. sodium bicarbonate (10 ml) was added and the mixture was extracted with methylene chloride. The combined extracts were washed with satd. aq. sodium bicarbonate (10 ml) and the solvent evaporated *in vacuo*.

-222-

EXAMPLE 7

5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester



10 The title compound is prepared in accordance with WO
94/10138 published on May 11, 1994, incorporated by reference.

BIOLOGICAL ASSAYS.

The ability of compounds of the present invention to inhibit cancer can be demonstrated using the following assays.

15

Raf kinase assay

Raf kinase activity *in vitro* is measured by the phosphorylation of its physiological substrate MEK (Map/ERK kinase). Phosphorylated MEK is subsequently trapped on a filter membrane and
20 incorporation of radio-labeled phosphate is quantitated by scintillation counting.

-223-

MATERIALS

Activated Raf

Produced in Sf9 insect cells coinfecting with three
5 different baculoviruses expressing epitope-tagged Raf, and the upstream
activators Val¹²-H-Ras, and Lck. The epitope sequence Glu-Tyr-Met-
Pro-Met-Glu ("Glu-Glu") was fused to the carboxy-terminus of full-
length c-Raf.

10 MEK

Catalytically inactive MEK is produced in Sf9 cells infected
with baculovirus expressing epitope-tagged MEK with a lysine⁹⁷ to
alanine mutation (K97A). The epitope sequence Glu-Tyr-Met-Pro-Met-
15 Glu ("Glu-Glu") was fused to the amino-terminus of full-length MEK1.

Anti "Glu-Glu" antibody

A hybridoma cell line expressing an antibody specific for
the "Glu-Glu" epitope was obtained from Gernot Walter, UCSD. Cells
were grown and antibodies were purified as described (Grussenmeyer
20 et al., Proc. Natl. Acad. Sci. U.S.A., 82, pp. 7952-7954, 1985).

Column buffer

20 mM Tris, pH 8, 100 mM NaCl, 1 mM EDTA, 2.5 mM
EGTA, 10 mM MgCl₂, 2 mM DTT, 0.4 mM AEBSF, 0.1% n-octyl
25 glucopyranoside, 1 nM okadaic acid, and 10 µg/ml each of benzamidine,
leupeptin, pepstatin, and aprotinin (all SIGMA).

5x reaction buffer

125 mM HEPES pH=8.0, 25 mM MgCl₂, 5 mM EDTA, 5
30 mM Na₃VO₄, 100 µg/ml BSA

Enzyme dilution buffer

25 mM HEPES pH=8.0, 1 mM EDTA, 1 mM Na₃VO₄, 400
µg/ml BSA.

35

Stop solution

100 mM EDTA, 80 mM sodium pyrophosphate.

-224-

Filter plates

Millipore Multiscreen #SE3M078E3, Immobilon-P (PVDF).

5

METHOD**A. Protein purification**

1. Sf9 insect cells were infected with baculovirus and grown as described (Williams et al., Proc. Natl. Acad. Sci. U.S.A., 89, pp. 2922-2926, 1992).
2. All subsequent steps were performed on ice or at 4°C. Cells were pelleted and lysed by sonication in column buffer. Lysates were spun at 17,000x g for 20 min, followed by 0.22 µm filtration.
3. Epitope-tagged proteins were purified by chromatography over a GammaBind Plus (Pharmacia) affinity column to which "Glu-Glu" antibody had been coupled. Proteins were loaded on the column, followed by washes with two column volumes of column buffer, and eluted with 50 µg/ml of peptide antigen (Glu-Tyr-Met-Pro-Met-Glu) in column buffer.

B. Raf kinase assay

1. Add 10 µl of inhibitor or control in 10% DMSO to assay plate.
2. Add 30 µl of reaction mix containing 10 µl 5x reaction buffer and 0.5 µl 1mM ³³P-γ-ATP (20 µCi/ml), 0.5 µl MEK (2.5 mg/ml), 1 µl 50 mM β-mercaptoethanol.
3. Start reaction by addition of 10 µl enzyme dilution buffer containing 1 mM DTT and an empirically determined amount of activated Raf that produces linear incorporation kinetics over the reaction time course.
4. Mix and incubate at room temperature for 90 min.
5. Stop reaction by addition of 50 µl stop solution.
6. Prewet filter plate with 70% ethanol and rinse with water.

-225-

7. Transfer 90 μ l aliquots of stopped reaction to filter plate.
8. Aspirate and wash four times with 200 μ l H₂O.
9. Add 50 μ l scintillation cocktail, seal plate, and count in Packard TopCount scintillation counter.

5

Map Kinase Phosphorylation assay

Inhibition of Raf kinase activity in intact cells is measured by determining the phosphorylation state of Map Kinase in TPA-stimulated C-33a human epithelial cells. Phosphorylated Map Kinase is detected by "Western" blot using an anti-phospho-Map Kinase antibody.

10

Materials

C33a Human Epithelial Cells

The C33a cell line is obtained from the ATCC repository, catalog # H TB31, and is maintained in DMEM (Mediatech) + 10% fetal bovine serum + 1% penicillin/streptomycin (Gibco) according to the instructions provided.

15

Anti-phospho-MAP Kinase antibody

The rabbit polyclonal anti-phospho-MAP kinase antibody is obtained from New England Biolabs (Beverly, MA)

20

Secondary antibody

The anti-rabbit antibody-alkaline phosphatase conjugate is obtained from New England Biolabs

25

Acrylamide Gel

Ten percent *bis*-acrylamide electrophoresis gels were obtained from Novex.

30

Blocking Buffer

1x Phosphate-buffered saline, 0.1% Tween-20, 5% nonfat dry milk.

-226-

Antibody dilution buffer

1x phosphate-buffered saline, 0.05% Tween-20, 5% bovine serum albumin

5 Alkaline phosphatase substrate

The chemiluminescent alkaline phosphatase substrate, CDP-Star™, is obtained from New England Biolabs.

Assay Buffer

10 0.1 M diethanolamine, 1 mM MgCl₂.

Method

1. C33a cells are grown to confluency in 24 well plates, then starved for
15 24 hr in DMEM + 0.5 % charcoal-stripped serum.

2. Compound to be tested, dissolved in DMSO at 1000x concentration, is added to each well.

20 3. One hour later, TPA (dissolved in DMSO at 1000x concentration) is added at a final concentration of 100 ng/ml.

4. Twenty minutes later, the media is removed from all wells, and 100 µl of boiling hot reducing Laemmli sample buffer is added to each well.
25 The plate is agitated, and the cell lysate is transferred to a 1.5 ml plastic microcentrifuge tube. Each lysate is then sonicated for 10 s, and placed in a boiling water bath for 5-10 minutes. Fifteen microliters of each sample is then loaded on a 10 % Laemmli polyacrylamide gel (Novex), and the gel electrophoresed according to the manufacturer's
30 instructions.

5. Proteins in the gel are electroblotted to a PVDF membrane, which is then rinsed in PBS and blocked with Blocking Buffer for approximately 1 hr at room temperature.

-227-

6. The PVDF membrane is rinsed in PBS. The anti-phospho-MapK antibody, diluted approximately 1:500 in antibody dilution buffer, is incubated with the PVDF membrane with gentle agitation overnight at 4 °C.

7. The PVDF membrane is rinsed 3 times for 5 minutes with Blocking Buffer, then incubated with the secondary antibody, diluted approximately 1 : 1000 in antibody dilution buffer, for 1 hr with gentle agitation at room temperature.

8. The PVDF membrane is rinsed 5 times for 5 minutes with Blocking Buffer, then incubated with the chemiluminescent alkaline phosphatase substrate dissolved in Assay Buffer for approximately 5 minutes. The membrane is then rinsed, wrapped in plastic, and exposed to x-ray film to detect blotted proteins.

In the Raf kinase inhibition assay, the IC₅₀ ranges from about 0.001 μM to about 1.5 μM.

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase.

Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber *et al.*, *J. Biol. Chem.* 265:14701-14704 (1990), Pompliano, *et al.*, *Biochemistry* 31:3800 (1992) and Gibbs *et al.*, *PNAS U.S.A.* 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 μl containing 100 mM N-(2-hydroxy ethyl) piperazine-N'-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM MgCl₂, 5 mM dithiothreitol (DTT), 100 mM [³H]-farnesyl diphosphate ([³H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 μg/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected

-228-

onto filter-mats using a TomTec Mach II cell harvester, washed with 100% ethanol, dried and counted in an LKB β -plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^3H]-FPP was utilized during the reaction period.

- 5 Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

- 10 Human FPTase was prepared as described by Omer *et al.*, Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μM ZnCl_2 and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min.,
15 stopped with 100 μl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

- The farnesyl protein transferase inhibiting compounds are tested for inhibitory activity against human FPTase by the assay described above and the compounds can generally be found to have
20 IC_{50} of approximately 50 μM .

In vivo ras farnesylation assay

- The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The
25 assay is performed essentially as described in DeClue, J.E. *et al.*, Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400
30 $\text{mCi}[^{35}\text{S}]$ methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl_2 /1 mM DTT/10 mg/ml aprotinin/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at

-229-

100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, J. *Viro.* 43:294-304, 5 (1982)). Following a 2 hour antibody incubation at 4°C, 200 µl of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 mM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100/0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE 10 sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

15

In vivo growth inhibition assay

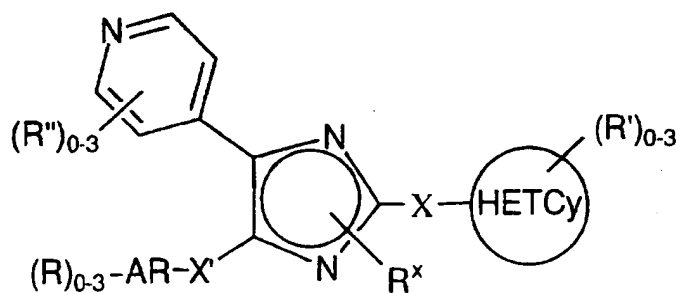
To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a 20 *v-ras*, *v-raf*, or *v-mos* oncogene is tested. Cells transformed by *v-Raf* and *v-Mos* may be included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either *v-ras*, *v-raf*, or *v-mos* are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in 25 a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). 30 The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

-230-

WHAT IS CLAIMED IS:

1. A method of treating cancer comprising administering to a mammalian patient in need of such treatment an effective amount of a RAF antagonist compound and an effective amount of a farnesyl protein transferase inhibiting compound.
2. A method of treating cancer in accordance with claim 1 wherein the cancer is selected from the group consisting of: cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.
3. A method of treating cancer in accordance with claim 1 wherein the cancer is selected from the group consisting of: histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers.
4. A method of treating cancer in accordance with claim 1 wherein the cancer is selected from the group consisting of: pancreatic and breast carcinoma.
5. A method of treating cancer in accordance with claim 1 wherein the RAF antagonist compound is selected from the group consisting of:
 - (a) a compound represented by formula (I-a):



(I-a)

-231-

or a pharmaceutically acceptable salt thereof, wherein:

5 AR represents an aromatic group containing 6-10 atoms;

X and X' each independently represent $-(CH_2)_m-Y-(CH_2)_n-$,
 wherein m and n represent integers within the range of from 0 - 4, such
 that the sum of m and n is from 0 - 6; Y represents a member selected
 from the group consisting of: a direct bond; O; $S(O)_y$, with y equal to
 10 0, 1 or 2; $NR^{q'}$, with $R^{q'}$ as defined below; $C(O)$; $OC(O)$; $C(O)O$;
 $SO_xNR^{q'}$ with x equal to 1 or 2 and $R^{q'}$ as defined below; $NR^{q'}SO_x$;
 $C(O)NR^{q'}$ and $NR^{q'}C(O)$;



represents a 4 to 10 membered non-aromatic
 heterocycle containing at least one N atom, and optionally containing
 1-2 additional N atoms and 0-1 O or S atom;

15 R^x represents H, C_{1-6} alkyl(R^q)₃, OC_{1-6} alkyl(R^q)₃ or
 $C(O)C_{1-6}$ alkyl(R^q)₃;

each R and R" independently represents a member selected
 from the group consisting of: halo; hydroxy; C_{1-6} alkyl(R^q)₃;
 20 OC_{1-6} alkyl(R^q)₃; C_{3-8} cycloalkyl(R^q)₃; CN; $CONH_2$; $CONHC_{1-6}$
 alkyl(R^q)₃; $CON(C_{1-6}$ alkyl(R^q)₃)₂; NH_2 ; NHC_{1-6} alkyl(R^q)₃;
 $N(C_{1-6}$ alkyl(R^q)₃)₂; CO_2H ; CO_2C_{1-6} alkyl(R^q)₃; $C(O)C_{1-6}$
 alkyl(R^q)₃; aryl(R^q)₃; heteroaryl(R^q)₃; CF_3 ; SH; NO_2 ; SO_yC_{1-6}
 alkyl(R^q)₃, with y as defined above; SO_2NH_2 ; SO_2NHC_{1-6} alkyl(R^q)₃;
 25 $SO_2N(C_{1-6}$ alkyl(R^q)₃)₂; $NHSO_2C_{1-6}$ alkyl(R^q)₃, $NHSO_2$ aryl(R^q)₃,
 $NHSO_2$ heteroaryl(R^q)₃, $N(R^q)C(O)C_{1-6}$ alkyl(R^q)₃; $NR^{q'}C(O)NH(C_{1-6}$
 alkyl(R^q)₃); C_{2-4} alkenyl(R^q)₂₋₃ and C_{2-4} alkynyl(R^q)₁₋₃;

-232-

each R' independently represents a member selected from the group consisting of: CONH₂; CONHC₁₋₆ alkyl(R^q)₃; CON(C₁₋₆ alkyl(R^q)₃)₂; CONHC₃₋₈ cycloalkyl(R^q)₃; CON(C₃₋₈ cycloalkyl(R^q)₃)₂; CO₂H; CO₂C₁₋₆ alkyl(R^q)₃; C(O)C₁₋₆ alkyl(R^q)₃; CO₂C₃₋₈ cycloalkyl(R^q)₃; C(O)C₃₋₈ cycloalkyl(R^q)₃; -[C(O)(CH₂)_j-CR⁵R⁶-(CH₂)_k-NR⁷]_p-R⁸; -C(O)C₃₋₈ cycloalkyl(R^q)₃; -C(O)heterocyclyl(R^q)₃; CON[C₁₋₆ alkyl(R^q)₃][C₃₋₈ cycloalkyl(R^q)₃]; C(O)aryl(R^q)₃; C(O)heteroaryl(R^q)₃;

10

wherein p represents 1, 2 or 3;

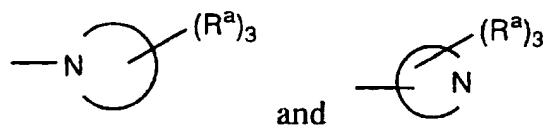
j and k are integers independently selected from 0 - 3;

each R⁵ and R⁶ independently represents H, aryl, C₁₋₆ alkyl(R^q)₃, or each CR⁵R⁶ taken in combination represents a 3, 4, 5 or 6 membered cycloalkyl or heterocyclyl group, an aryl group or a heteroaryl group, wherein when p equals 1, at least one of j and k is 1, 2 or 3;

each R⁷ and R⁸ independently represents H, C₁₋₆ alkyl or aryl;

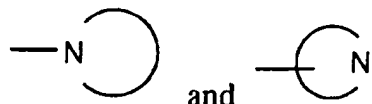
R^q represents a member selected from the group consisting of: R^{q'}; CN; CO₂H; CO₂C₁₋₄ alkyl; C(O)C₁₋₄ alkyl; aryl(R^a)₃; NH₂; NHC₁₋₆ alkyl(R^a)₃; N(C₁₋₆ alkyl(R^a)₃)₂; heteroaryl(R^a)₃; CONH₂; SH; S(O)_y C₁₋₆ alkyl(R^a)₃; C(O)NHC₁₋₆ alkyl(R^a)₃; C(O)N(C₁₋₆ alkyl(R^a)₃)₂; -heteroalkyl(R^a)₃; -NHC(O)NH₂; -NHC(NH)NH₂;

30



-233-

wherein

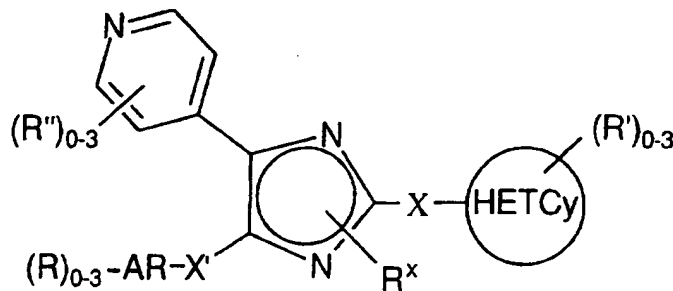


and independently represent mono or bicyclic ring systems, non-aromatic or partially aromatic, containing from 5-10 ring atoms, 1-4 of which are N and 0-1 of which are O or S(O)_y, with y equal to 0, 1 or 2, optionally containing 1-2 carbonyl groups;

each R^a independently represents a member selected from the group consisting of: H, C₁₋₆ alkyl, OC₁₋₆ alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aralkoxy, substituted aralkoxy, halo, hydroxy, CN, CONH₂, CONHC₁₋₆ alkyl, CON(C₁₋₆ alkyl)₂, CO₂H, CO₂C₁₋₆ alkyl, C(O)C₁₋₆ alkyl, phenyl, CF₃, SH, NO₂, SO_yC₁₋₆ alkyl, with y as defined above; SO₂NH₂, SO₂NHC₁₋₆ alkyl, NHSO₂(substituted aryl), NHSO₂(substituted heteroaryl), NHSO₂C₁₋₆ alkyl, NHSO₂aryl, NHSO₂heteroaryl, NH₂, NHC₁₋₆ alkyl, N(C₁₋₆ alkyl)₂, NHC(O)C₁₋₆ alkyl, NHC(O)NH(C₁₋₆ alkyl), C₂₋₄ alkenyl and C₂₋₄ alkynyl;

and R^{q'} represents H, OH, C₁₋₄ alkyl, -OC₁₋₄ alkyl, aryl or C(O)C₁₋₄ alkyl;

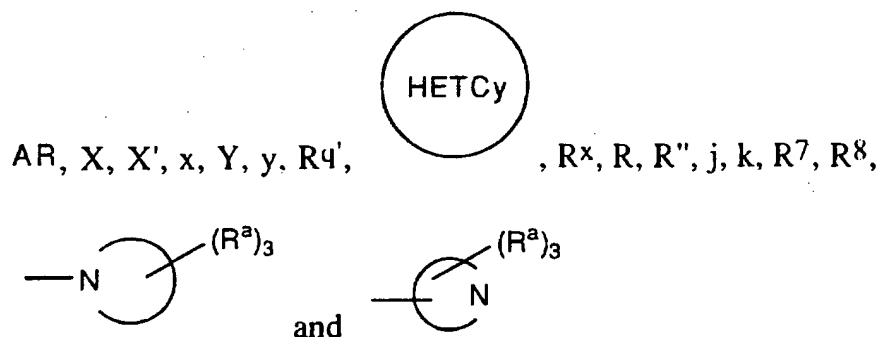
(b) a compound represented by formula (I-b):



(I-b)

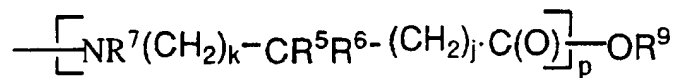
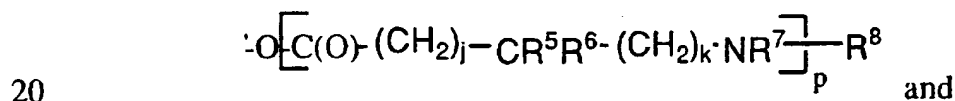
or a pharmaceutically acceptable salt thereof, wherein:

-234-



5 are as defined above with respect to formula (I-a);

each R' independently represents a member selected from the group consisting of: hydroxy; C₁₋₆ alkyl(R^q)₃; C₃₋₈ cycloalkyl(R^q)₃; OC₁₋₆ alkyl(R^q)₃; OC₃₋₈ cycloalkyl(R^q)₃; heterocyclyl(R^q)₃; CN; NH(R^{q''}); NHC₁₋₆ alkyl(R^q)₃; N(C₁₋₆ alkyl(R^q)₃)₂; NHC₃₋₈ cycloalkyl(R^q)₃; N(C₃₋₈ cycloalkyl(R^q)₃)₂; CF₃; SH; NO₂; C₂₋₄ alkenyl(R^q)₂₋₃, aryl(R^q)₃, heteroaryl(R^q)₃; C₂₋₄ alkynyl(R^q)₁₋₃; -OC(O) C₃₋₈ cycloalkyl(R^q)₃; SO₂NH₂; SO₂NHC₁₋₆ alkyl(R^q)₃; SO₂N(C₁₋₆ alkyl(R^q)₃)₂; NHSO₂C₁₋₆alkyl(R^q)₃, NHSO₂aryl(R^q)₃, NHSO₂heteroaryl(R^q)₃, -OC(O)heterocyclyl(R^q)₃; N(R^{q'})C(O)C₁₋₆ alkyl(R^q)₃; NR^{q'}C(O)NH(C₁₋₆ alkyl(R^q)₃); -OC(O)C₁₋₆ alkyl(R^q)₃; -OC(O)aryl(R^q)₃, -OC(O)heteroaryl(R^q)₃; -C(=NR^{q'})NH₂; -C(=N^{q'})NHC₁₋₆ alkyl(R^q)₃, -C(=N^{q'})N(C₁₋₆ alkyl(R^q)₃)₂;



25 R⁵ and R⁶ are independently H, aryl, C₁₋₆ alkyl(R^q)₃, or CR⁵R⁶ in combination represents a 3, 4, 5 or 6 membered cycloalkyl or heterocyclyl group, an aryl group or a heteroaryl group;

-235-

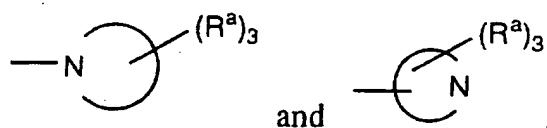
p represents 1, 2 or 3, with the proviso that when p represents 1, CR⁵R⁶ represents a 3, 4, 5 or 6 membered cycloalkyl group or a heterocyclyl group, an aryl group or a heteroaryl group, and at least one of j and k is 1, 2 or 3;

5

R⁹ represents H, a negative charge balanced by a positively charged group or a protecting group;

10 R⁹ represents a member selected from the group consisting of: R^{q'}; CN; CO₂H; CO₂C₁₋₄ alkyl; C(O)C₁₋₄ alkyl; NH(R^{q''}); aryl(R^a)₃; heteroaryl(R^a)₃; NHC₁₋₄ alkyl; N(C₁₋₄ alkyl)₂; CONH₂; SH; S(O)_y C₁₋₆ alkyl(R^a)₃; C(O)NHC₁₋₆ alkyl(R^a)₃; C(O)N(C₁₋₆ alkyl(R^a)₃)₂; NHC(NH)NH₂; -heteroalkyl(R^a)₃; -NHC(O)NH₂;

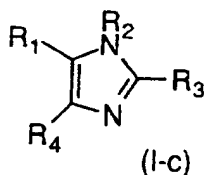
15



and

and R^{q''} represents H, OH or OC₁₋₄ alkyl;

20 and (c) a compound represented by formula (I-c):



or a pharmaceutically acceptable salt thereof,

25 wherein:

R₁ is 4-pyridyl, pyrimidinyl, quinazolin-4-yl, quinolyl, isoquinolinyl, 1-imidazolyl or 1-benzimidazolyl which is optionally substituted with one or two substituents each of which is independently selected from C₁₋₄ alkyl, halogen, C₁₋₄ alkoxy, C₁₋₄ alkylthio, NR₁₀R₂₀, or N-heterocyclyl ring which ring has from 5 to 7 members and optionally

30

-236-

contains an additional heteroatom selected from oxygen, sulfur or NR₂₂;

- R₂ is hydrogen, -(CR₁₀R₂₀)_n OR₁₂, heterocyclyl, heterocyclyl C₁-10 alkyl, C₁-10 alkyl, halo-substituted C₁-10 alkyl, C₂-10 alkenyl, C₂-10 alkynyl, C₃-7 cycloalkyl, C₃-7 cycloalkyl C₁-10 alkyl, C₅-7 cycloalkenyl, aryl, aryl C₁-10 alkyl, heteroaryl, heteroaryl C₁-10 alkyl, (CR₁₀R₂₀)_n'OR₁₃, (CR₁₀R₂₀)_n'S(O)_mR₂₅, (CR₁₀R₂₀)_n'NHS(O)₂R₂₅, (CR₁₀R₂₀)_n'NR₈R₉, (CR₁₀R₂₀)_n'NO₂, (CR₁₀R₂₀)_n'CN, (CR₁₀R₂₀)_n'S(O)_mNR₈R₉, (CR₁₀R₂₀)_n'C(Z)R₁₃, (CR₁₀R₂₀)_n'C(Z)OR₁₃, (CR₁₀R₂₀)_n'NR₁₀C(Z)NR₈R₉, (CR₁₀R₂₀)_n'C(Z)NR₁₃OR₁₂, (CR₁₀R₂₀)_n'NR₁₀C(Z)R₁₃, (CR₁₀R₂₀)_n'NR₁₀C(Z)NR₈R₉, (CR₁₀R₂₀)_n'N(OR₂₁)C(Z)NR₈R₉, (CR₁₀R₂₀)_n'N(OR₂₁)C(Z)R₁₃, (CR₁₀R₂₀)_n'C(=NOR₂₁)R₁₃, (CR₁₀R₂₀)_n'NR₁₀C(=NR₂₇)NR₈R₉, (CR₁₀R₂₀)_n'OC(Z)NR₈R₉, (CR₁₀R₂₀)_n'NR₁₀C(Z)NR₈R₉, (CR₁₀R₂₀)_n'C(Z)OR₁₀, 5-(R₂₅)-1,2,4-oxadiazol-3-yl or 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl moieties may be optionally substituted;
- n' is an integer having a value of 1 to 10;
m is 0 or the integer 1 or 2;
R₃ is Q-(Y₁)_t;
Q is an aryl or heteroaryl group;
t is a number having a value of 1, 2 or 3;
- Z is oxygen or sulfur;
n is 0 or an integer from 1 to 10;
Y₁ is independently selected from hydrogen, C₁-5 alkyl, halo-substituted C₁-5 alkyl, halogen, or -(CR₁₀R₂₀)_nY₂;
Y₂ is -OR₈, -NO₂, -S(O)_m'R₁₁, -SR₈, -S(O)_m'OR₈, -S(O)_mNR₈R₉, -NR₈R₉, -O(CR₁₀R₂₀)_nNR₈R₉, -C(O)R₈, -CO₂R₈, -CO₂(CR₁₀R₂₀)_nCONR₈R₉, -ZC(O)R₈, -CN, -C(Z)NR₈R₉, NR-NR₁₀C(Z)R₈, -C(Z)NR₈OR₉, -NR₁₀C(Z)NR₈R₉, -NR₁₀S(O)_mR₁₁, -N(OR₂₁)C(Z)NR₈R₉, -N(OR₂₁)C(Z)R₈, -C(=NOR₂₁)R₈, -NR₁₀C(=NR₁₅)SR₁₁, -NR₁₀C(=NR₁₅)NR₈R₉,

-237-

- NR₁₀C(=CR₁₄R₂₄)SR₁₁, -NR₁₀C(=CR₁₄R₂₄)NR₈R₉,
 -NR₁₀C(O)C(O)NR₈R₉, -NR₁₀C(O)C(O)OR₁₀,
 -C(=NR₁₃)NR₈R₉, -C(=NOR₁₃)NR₈R₉, -C(=NR₁₃)ZR₁₁,
 -OC(Z)NR₈R₉, -NR₁₀S(O)_mCF₃, -NR₁₀C(Z)OR₁₀, 5-(R₁₈)-
 1,2,4-oxadizaol-3-yl or 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-
 oxadiazol-3-yl;
 m' is a number having a value of 1 or 2;
 R₄ is phenyl, naphth-1-yl or naphth-2-yl which is optionally substituted
 by one or two substituents, each of which is independently selected,
 and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-1-yl
 substituent, is halo, cyano, -C(Z)NR₇R₁₇, -C(Z)OR₂₃,
 -(CR₁₀R₂₀)_m^{m'}COR₃₆, SR₅, -SOR₅, OR₃₆, halo-substituted-C₁₋₄
 alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃ or
 -(CR₁₀R₂₀)_m^{m'}NR₁₀R₂₀ and which, for other positions of
 substitution, is halo, cyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈,
 -(CR₁₀R₂₀)_m^{m'}COR₈, -S(O)_mR₈, -OR₈, halo-substituted-C₁₋₄
 alkyl, C₁₋₄ alkyl, -(CR₁₀R₂₀)_m^{m'}NR₁₀C(Z)R₈, -NR₁₀S(O)_mR₁₁,
 -NR₁₀S(O)_mNR₇R₁₇, -ZC(Z)R₈ or -(CR₁₀R₂₀)_m^{m'}NR₁₆R₂₆;
 wherein m" is 0 to 5 and m'" is 0 or 1;
 R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇,
 excluding the moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being
 -SOH;
 R₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkenyl, C₂₋₄
 alkynyl or C₃₋₅ cycloalkyl;
 R₇ and R₁₇ are each independently selected from hydrogen or C₁₋₄
 alkyl, or R₇ and R₁₇ together with the nitrogen to which they are
 attached form a heterocyclic ring of 5 to 7 members which ring
 optionally contains an additional heteroatom selected from oxygen,
 sulfur or NR₂₂;
 R₈ is hydrogen, heterocyclyl, heterocyclylalkyl or R₁₁;
 R₉ is hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇
 cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylalkyl, heteroaryl or
 heteroarylalkyl or R₈ and R₉ may together with the nitrogen to
 which they are attached form a heterocyclic ring of 5 to 7 members

-238-

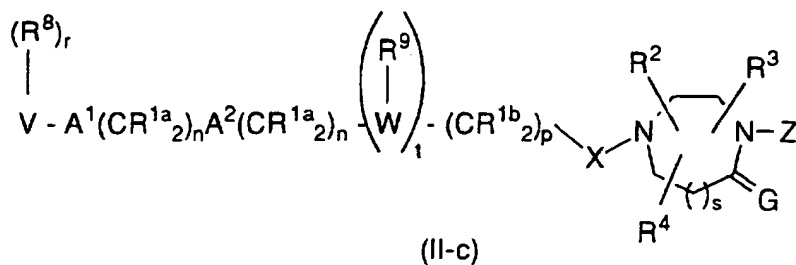
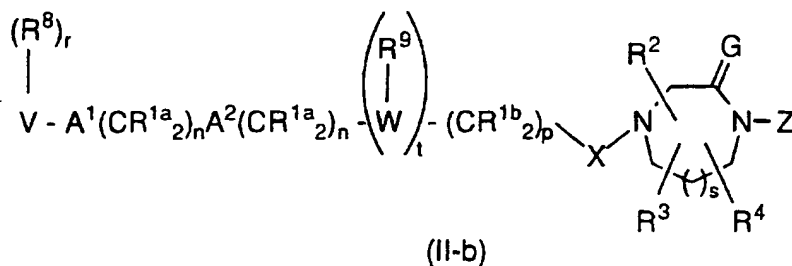
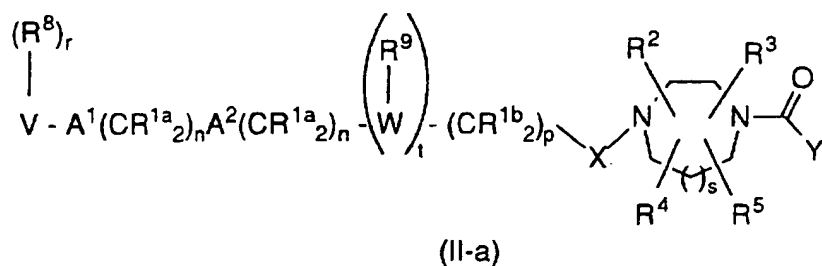
- which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;
- R₁₀ and R₂₀ are each independently selected from hydrogen and C₁₋₄ alkyl;
- 5 R₁₁ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
- R₁₂ is hydrogen, -C(Z)R₁₃ or optionally substituted C₁₋₄ alkyl, optionally substituted arylC₁₋₄ alkyl or S(O)₂R₂₅;
- 10 R₁₃ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀ alkyl, aryl, aryl C₁₋₁₀ alkyl, heteroaryl or heteroaryl C₁₋₁₀ alkyl;
- R₁₄ and R₂₄ is each independently selected from hydrogen, alkyl, nitro or cyano;
- 15 R₁₅ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;
- R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members
- 20 which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;
- R₁₈ and R₁₉ is each independently selected from hydrogen, C₁₋₄ alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together denote a oxygen or sulfur;
- 25 R₂₁ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;
- R₂₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;
- R₂₃ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl or C₃₋₅ cycloalkyl;
- 30 R₃₆ is hydrogen or R₂₃;
- R₂₅ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁₋₁₀ alkyl, heteroaryl or heteroarylalkyl;
- R₂₇ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl.

-239-

6. A method of treating cancer in accordance with claim 1 wherein the farnesyl transferase inhibiting compound is selected from the group consisting of:

5

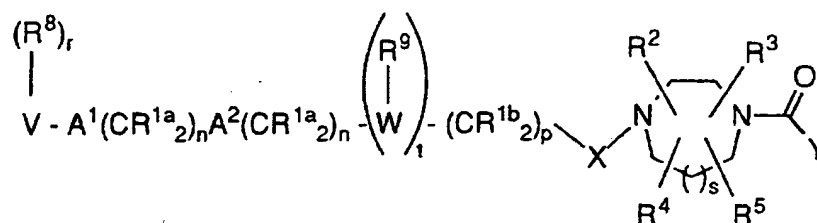
(a) a compound represented by one of formulas (II-a) through (II-c):



or a pharmaceutically acceptable salt thereof,

10 wherein with respect to formula (II-a):

-240-

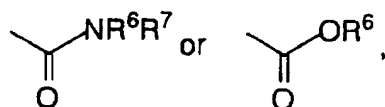


(II-a)

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl,
 5 C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN,
 NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃,
 $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆
 10 alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN,
 $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃,
 $-N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;

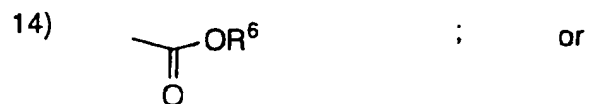
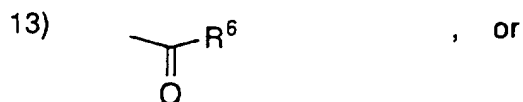
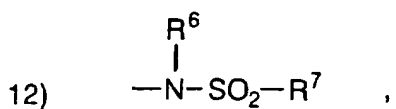
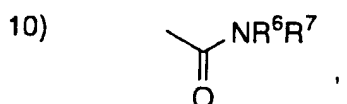
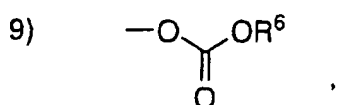
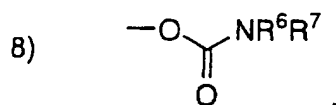
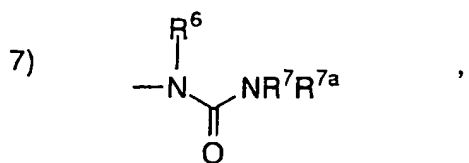
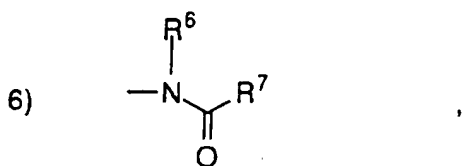
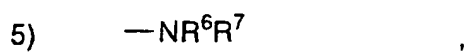
R^2 and R^3 are independently selected from: H; unsubstituted or
 15 substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl,
 unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,
 unsubstituted or substituted heterocycle,



wherein the substituted group is substituted with one or more of:

- 20 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁-4 alkyl,
 - b) $(CH_2)_pOR^6$,
 - c) $(CH_2)_pNR^6R^7$,
 - d) halogen,
- 25 2) C₃-6 cycloalkyl,
- 3) OR^6 ,
- 4) SR^6 , $S(O)R^6$, SO_2R^6 .

-241-



5
10 R² and R³ are attached to the same C atom and are combined to form - (CH₂)_u - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

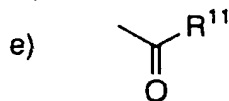
-242-

R^4 and R^5 are independently selected from H and CH_3 ;

- 5 and any two of R^2 , R^3 , R^4 and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl,
 10 heteroarylsulfonyl, unsubstituted or substituted with:

- a) C_{1-4} alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,



- 15 f) $-SO_2R^{11}$, or
 g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
 R^7 and R^{7a} may be joined in a ring;

20

R^8 is independently selected from:

- a) hydrogen,
 b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl,
 C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$,
 25 $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $R^{10}_2N-C(NR^{10})-$,
 $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or
 $R^{11}OC(O)NR^{10}-$, and
 c) C_1-C_6 alkyl unsubstituted or substituted by aryl,
 heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6
 30 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$,

-243-

$R^{10}C(O)NH-$, CN , $H_2N-C(NH)-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{10}OC(O)NH-$;

R^9 is selected from:

- 5 a) hydrogen,
- b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , NO_2 , $(R^{10})_2N-C-(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
- 10 c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C-(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

- 15 R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

- 20 A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$, or $S(O)_m$;

V is selected from:

- 25 a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N,
- 30 and
- e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

-244-

W is a heterocycle;

X is $-\text{CH}_2-$, $-\text{C}(=\text{O})-$, or $-\text{S}(=\text{O})_m-$;

5 Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

- 1) C_{1-4} alkyl, unsubstituted or substituted with:
 - a) C_{1-4} alkoxy,
 - b) NR^6R^7 ,
 - 10 c) C_{3-6} cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO ,
 - f) $-\text{S}(\text{O})_m\text{R}^6$, or
 - g) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
- 15 2) aryl or heterocycle,
- 3) halogen,
- 4) OR^6 ,
- 5) NR^6R^7 ,
- 6) CN ,
- 20 7) NO_2 ,
- 8) CF_3 ;
- 9) $-\text{S}(\text{O})_m\text{R}^6$,
- 10) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, or
- 11) $\text{C}_3\text{-C}_6$ cycloalkyl;

25

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

r is 0 to 5, provided that r is 0 when V is hydrogen;

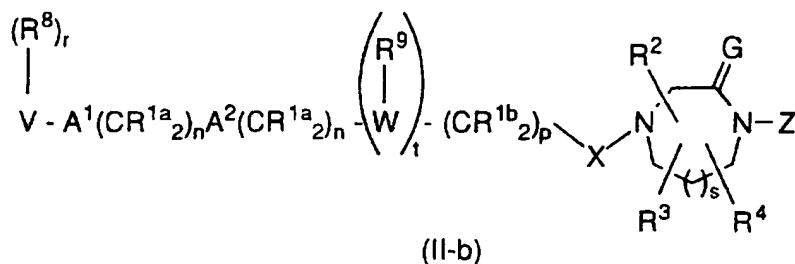
30 s is 0 or 1;

t is 0 or 1; and

u is 4 or 5;

with respect to formula (II-b):

-245-



R^{1a}, R^{1b}, R¹⁰, R¹¹, m, R², R³, R⁶, R⁷, p, R^{7a}, u, R⁸, A¹, A², V, W, X, n, p, r, s, t and u are as defined above with respect to formula (II-a);

5 R⁴ is selected from H and CH₃;

and any two of R², R³ and R⁴ are optionally attached to the same carbon atom;

10 R⁹ is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 15 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 20 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

20

G is H₂ or O;

Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

25

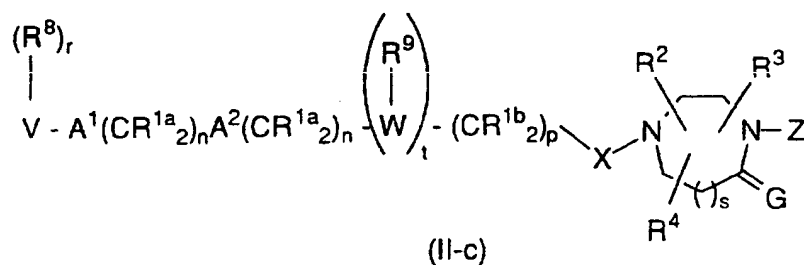
- 1) C₁-4 alkyl, unsubstituted or substituted with:
 - a) C₁-4 alkoxy,
 - b) NR⁶R⁷,
 - c) C₃-6 cycloalkyl,

-246-

- d) aryl or heterocycle,
 e) HO,
 f) $-S(O)_mR^6$, or
 g) $-C(O)NR^6R^7$,
- 5 2) aryl or heterocycle,
 3) halogen,
 4) OR^6 ,
 5) NR^6R^7 ,
 6) CN,
 10 7) NO_2 ,
 8) CF_3 ;
 9) $-S(O)_mR^6$,
 10) $-C(O)NR^6R^7$, or
 11) C_3-C_6 cycloalkyl;

15

with respect to formula (II-c):



R^{1a} , R^{1b} , R^{10} , R^{11} , m , R^2 , R^3 , R^6 , R^7 , p , u , R^{7a} , R^8 , A^1 , A^2 , V , W , X ,
 n , r and t are as defined above with respect to formula (II-a);

20

R^4 is selected from H and CH_3 ;

25. and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

G is O;

-247-

Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

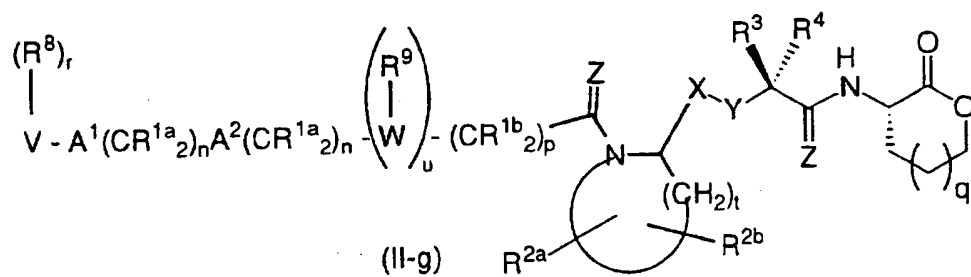
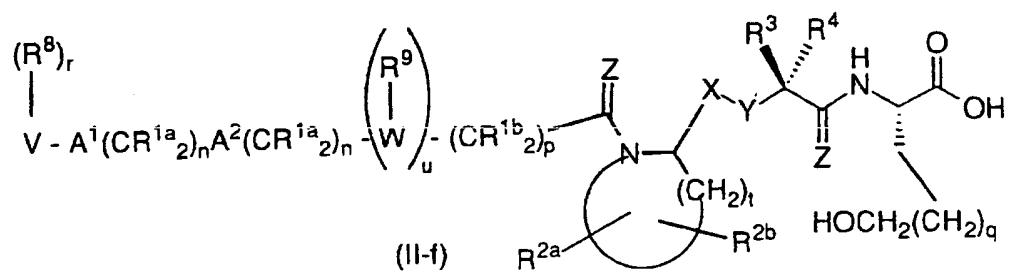
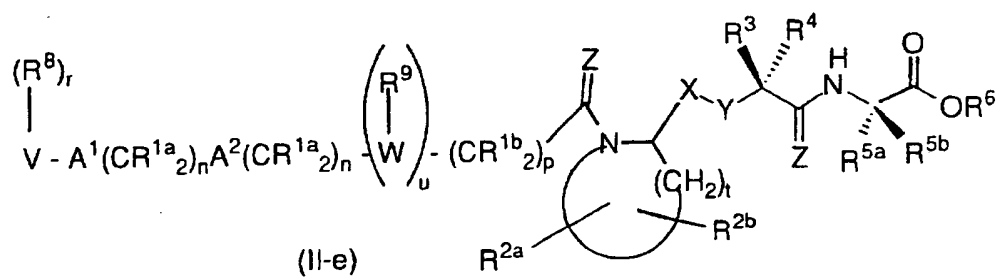
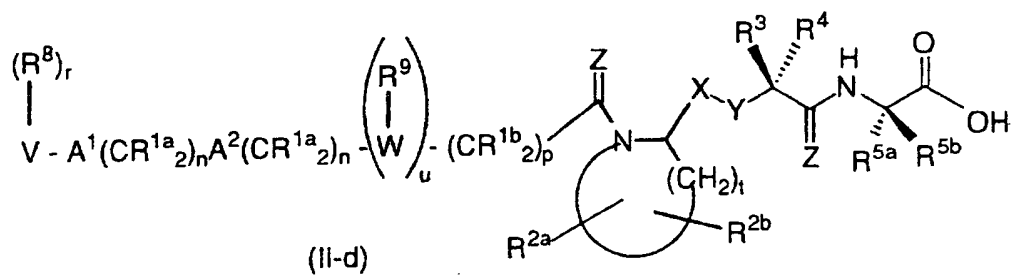
- 1) C₁₋₄ alkyl, unsubstituted or substituted with:
 - 5 a) C₁₋₄ alkoxy,
 - b) NR⁶R⁷,
 - c) C₃₋₆ cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - 10 f) -S(O)_mR⁶, or
 - g) -C(O)NR⁶R⁷,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR⁶,
- 15 5) NR⁶R⁷,
- 6) CN,
- 7) NO₂,
- 8) CF₃;
- 9) -S(O)_mR⁶,
- 20 10) -C(O)NR⁶R⁷, or
- 11) C₃₋₆ cycloalkyl;

and

25 s is 1;

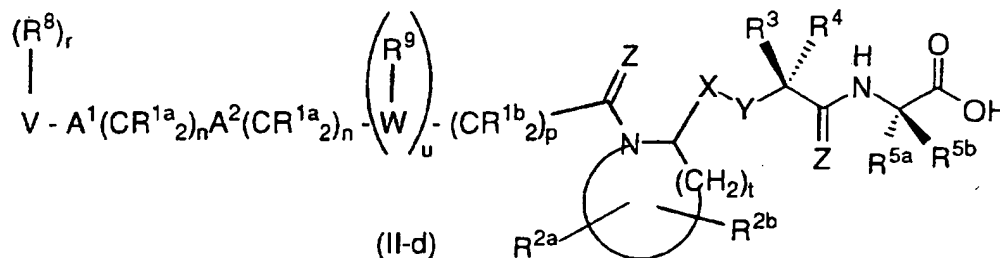
(b) a compound represented by formula (II-d) through (II-g):

-248-



5 wherein with respect to formula (II-d):

-249-



R^{11} , V , W , m , n , p and r are as defined above with respect to formula (II-a);

5

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N₃, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, $R^{10}O$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and

-250-

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

5 R³ and R⁴ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 10 ii) methionine sulfone, and
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,
 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 15 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-,
 N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
 and
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and
 20 C₃-C₁₀ cycloalkyl; or

R³ and R⁴ are combined to form - (CH₂)_s - ;

R^{5a} and R^{5b} are independently selected from:

- 25 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 30 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F, Cl, Br,
 CF₃, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-,
 R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,

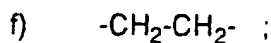
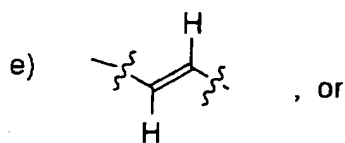
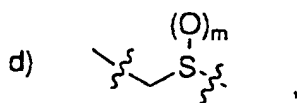
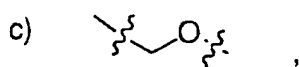
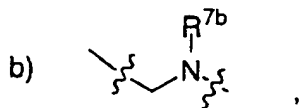
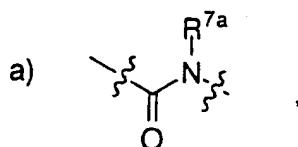
-251-

$R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and
 C_1-C_{20} alkyl,

- d) C_1-C_6 alkyl substituted with an unsubstituted or
substituted group selected from aryl, heterocycle and
 C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the
carbon atoms is optionally replaced by a moiety selected from: O,
 $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$;

X-Y is



R^{7a} is selected from

- 15 a) hydrogen,

-252-

- 5 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted
 or substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl;

R^{7b} is selected from

- 10 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted
 or substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl,
 15 f) a carbonyl group which is bonded to an unsubstituted or
 substituted group selected from aryl, heterocycle, C₃-C₁₀
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
 20 heterocycle and C₃-C₁₀ cycloalkyl, and
 g) a sulfonyl group which is bonded to an unsubstituted or
 substituted group selected from aryl, heterocycle, C₃-C₁₀
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
 25 heterocycle and C₃-C₁₀ cycloalkyl;

R⁸ is independently selected from:

- 30 a) hydrogen,
 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl,
 C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and

-253-

- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- 10 a) hydrogen,
 b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 15 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from H, C₁-C₆ alkyl, benzyl, substituted aryl and C₁-C₆ alkyl substituted with substituted aryl;

20 A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

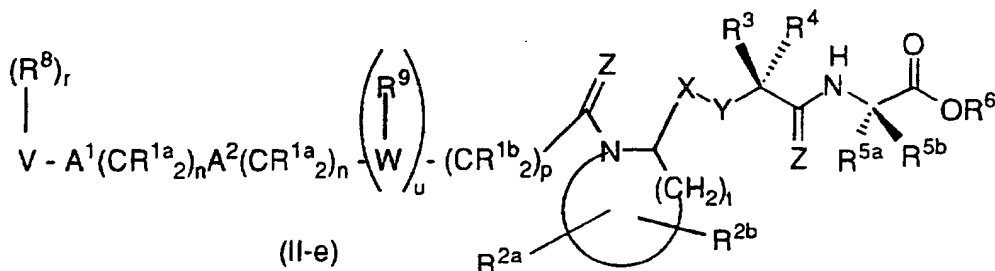
25 Z is independently H₂ or O;

s is 4 or 5;
 t is 3, 4 or 5; and
 u is 0 or 1;

30

with respect to formula (II-e):

-254-



R¹¹, W, m, n, p and r are as defined above with respect to formula (II-a);

5 R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 10 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 15 -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 20
- c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 25

-255-

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;
- 5 R³ and R⁴ are independently selected from:
- a) a side chain of a naturally occurring amino acid,
 - b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - 10 ii) methionine sulfone,
 - c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,

wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,

15 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 - d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and
 - 20 C₃-C₁₀ cycloalkyl; or

R³ and R⁴ are combined to form - (CH₂)_s - ;

- R^{5a} and R^{5b} are independently selected from:
- 25 a) a side chain of a naturally occurring amino acid,
 - b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
 - 30 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, CF₃, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,

-256-

$R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and
 C_1-C_{20} alkyl, and

- d) C_1-C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 C_3-C_{10} cycloalkyl; or

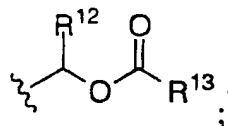
R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the
 carbon atoms is optionally replaced by a moiety selected from: O,
 $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$;

R^6 is

- a) substituted or unsubstituted C_1-C_8 alkyl, substituted or
 unsubstituted C_5-C_8 cycloalkyl, or substituted or
 unsubstituted cyclic amine, wherein the substituted alkyl,
 cycloalkyl or cyclic amine is substituted with 1 or 2
 substituents independently selected from:

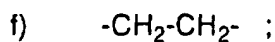
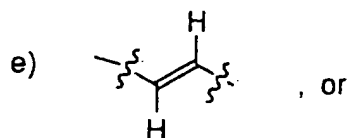
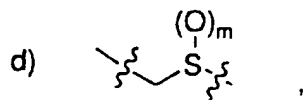
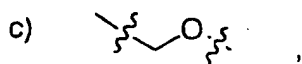
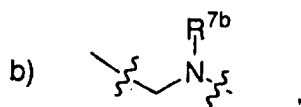
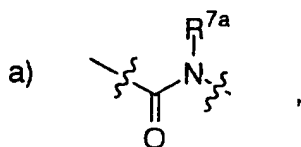
- 1) C_1-C_6 alkyl,
- 2) aryl,
- 3) heterocycle,
- 4) $-N(R^{11})_2$,
- 5) $-OR^{10}$, or

b)



-257-

X-Y is



5 R^{7a} is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
- 10 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

R^{7b} is selected from

- 15 a) hydrogen,
- b) unsubstituted or substituted aryl,

-258-

- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted
or substituted group selected from aryl, heterocycle and
C₃-C₁₀ cycloalkyl,
- f) a carbonyl group which is bonded to an unsubstituted or
substituted group selected from aryl, heterocycle, C₃-C₁₀
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocycle and C₃-C₁₀ cycloalkyl, and
- g) a sulfonyl group which is bonded to an unsubstituted or
substituted group selected from aryl, heterocycle, C₃-C₁₀
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocycle and C₃-C₁₀ cycloalkyl;

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl,
C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,
R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆
alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-,
N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl,

-259-

Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

5 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

10 R¹⁰ is independently selected from H, C₁-C₆ alkyl, benzyl, substituted aryl and C₁-C₆ alkyl substituted with substituted aryl;

R¹² is hydrogen or C₁-C₆ alkyl;

R¹³ is C₁-C₆ alkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

20 Z is independently H₂ or O;

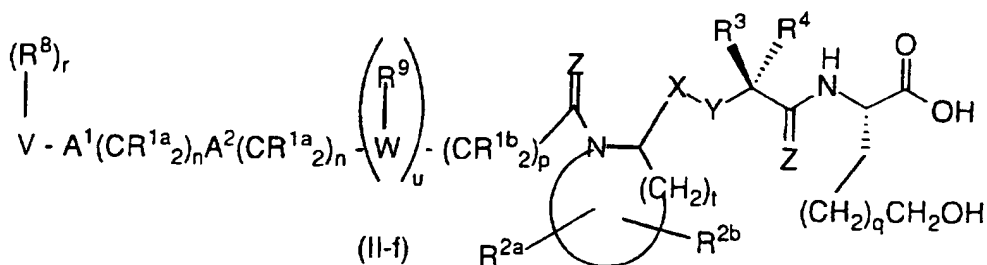
s is 4 or 5;

t is 3, 4 or 5; and

u is 0 or 1;

25

with respect to formula (II-f):



-260-

R^{11} , V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}-$,
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;
- 15 R^{2a} and R^{2b} are independently selected from:
 - a) hydrogen,
 - b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N₃, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
 - 20 c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO₂, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N₃, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
 - 25 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

R^3 and R^4 are independently selected from:

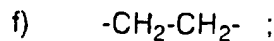
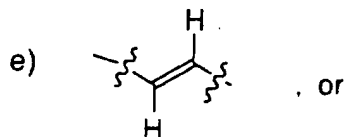
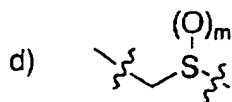
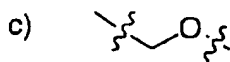
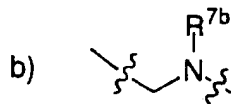
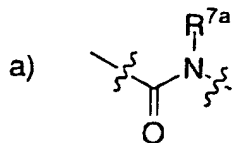
- 30 a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and

-261-

- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,
 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 5 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-,
 N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
 and
- d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 10 C₃-C₁₀ cycloalkyl; or

R³ and R⁴ are combined to form - (CH₂)_s - ;

X-Y is



-262-

R7a is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocycle,
- 5 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

10 R7b is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 15 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl,
- f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl, and
- 20 g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;
- 25

R8 is independently selected from:

- 30 a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,

-263-

$R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or
 $R^{11}OC(O)NR^{10}-$, and

- 5 c) C_1 - C_6 alkyl unsubstituted or substituted by aryl,
 heterocycle, C_3 - C_{10} cycloalkyl, C_2 - C_6 alkenyl, C_2 - C_6
 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$,
 $R^{10}C(O)NH-$, CN, $H_2N-C(NH)-$, $R^{10}C(O)-$, $R^{10}OC(O)-$,
 N_3 , $-N(R^{10})_2$, or $R^{10}OC(O)NH-$;

R^9 is selected from:

- 10 a) hydrogen,
 b) C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, perfluoroalkyl, F, Cl,
 Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 ,
 $(R^{10})_2N-C-(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
 15 c) C_1 - C_6 alkyl unsubstituted or substituted by perfluoroalkyl,
 F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN,
 $(R^{10})_2N-C-(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

- 20 R^{10} is independently selected from H, C_1 - C_6 alkyl, benzyl, substituted
 aryl and C_1 - C_6 alkyl substituted with substituted aryl;

R^{12} is hydrogen or C_1 - C_6 alkyl;

- 25 R^{13} is C_1 - C_6 alkyl;

A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$,
 $-C(O)-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$,
 $-N(R^{10})S(O)_2-$, or $S(O)_m$;

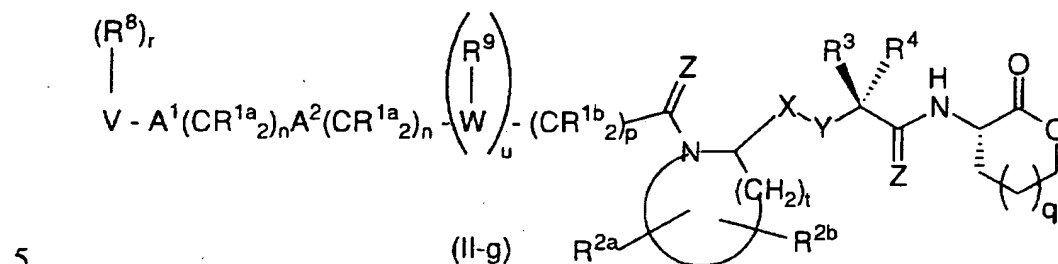
- 30 Z is independently H_2 or O;

q is 0, 1 or 2;
 s is 4 or 5;

-264-

t is 3, 4 or 5; and
u is 0 or 1;

with respect to formula (II-g):



R^{11} , V , W , m , n , p and r are as previously defined with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

- 10 a) hydrogen,
b) aryl, heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl,
C2-C6 alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
CN, NO_2 ,
(R^{10}) $_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
15 - $N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
c) C1-C6 alkyl unsubstituted or substituted by aryl,
heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6
alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN,
(R^{10}) $_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
20 - $N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
25 b) C1-C6 alkyl unsubstituted or substituted by C2-C6
alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N_3 ,
(R^{10}) $_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, - $N(R^{10})_2$, or
 $R^{11}OC(O)NR^{10}-$,

-265-

- c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰), R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂ or R¹¹OC(O)NR¹⁰-, and
- 5 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

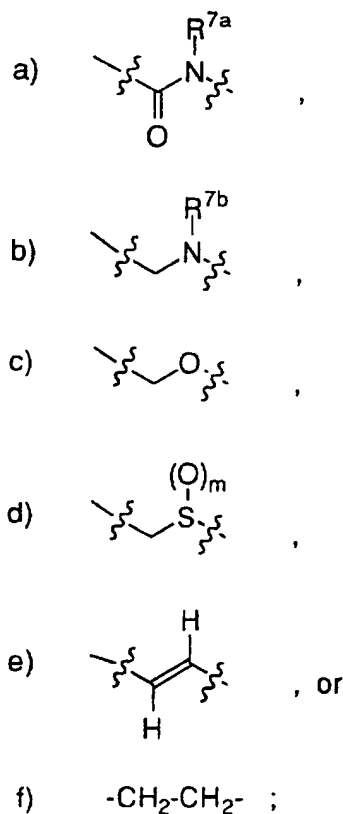
R³ and R⁴ are independently selected from:

- 10 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
- 15 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- 20 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or
- 25

R³ and R⁴ are combined to form - (CH₂)_s - ;

-266-

X-Y is

R^{7a} is selected from

- 5 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
 10 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted
 or substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl;

R^{7b} is selected from

- 15 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,

-267-

- d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl,
- 5 f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl, and
- 10 g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C₃-C₁₀ cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

15

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 20 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆
 25 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
 R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-,
 N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- 30 a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

-268-

- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

5

R¹⁰ is independently selected from H, C₁-C₆ alkyl, benzyl, substituted aryl and C₁-C₆ alkyl substituted with substituted aryl;

R¹² is hydrogen or C₁-C₆ alkyl;

10

R¹³ is C₁-C₆ alkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-,

15

-N(R¹⁰)S(O)₂-, or S(O)_m;

Z is independently H₂ or O;

q is 0, 1 or 2;

20

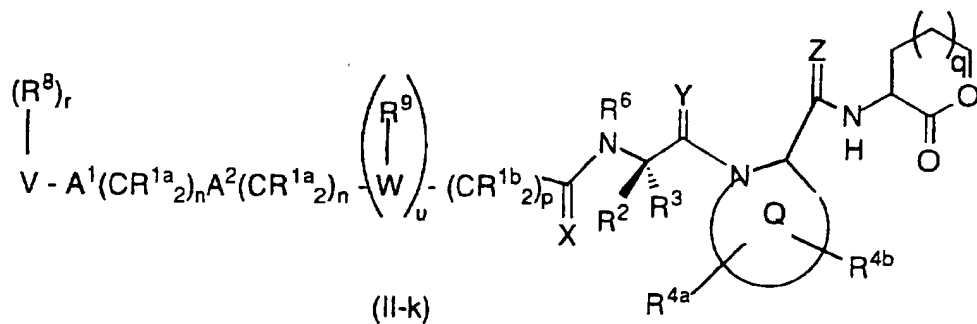
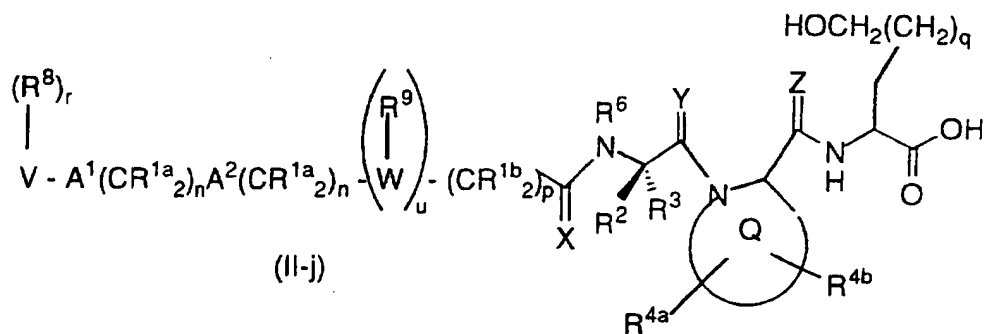
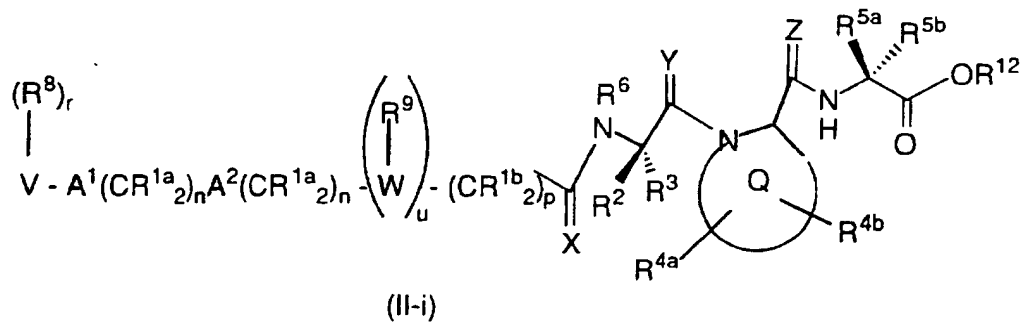
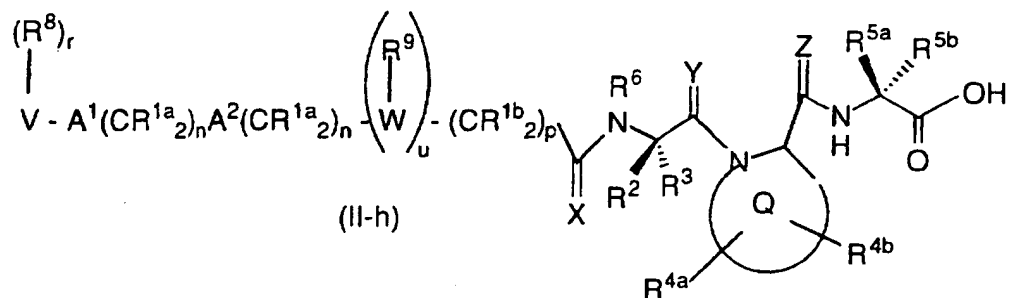
s is 4 or 5;

t is 3, 4 or 5; and

u is 0 or 1;

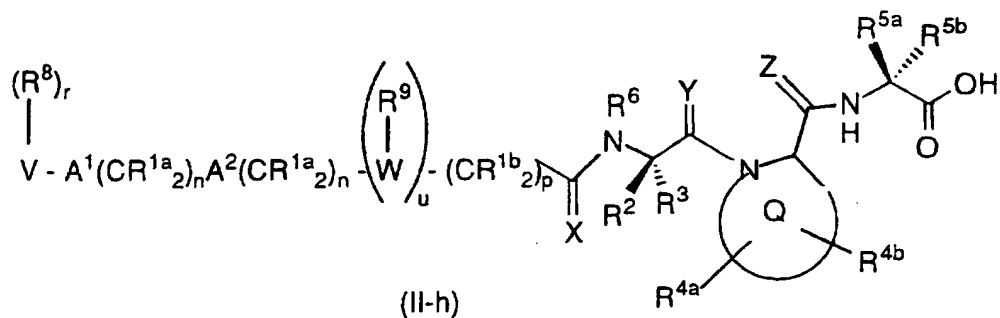
(c) a compound represented by one of formulas (II-h) through (II-k):

-269-



or a pharmaceutically acceptable salt thereof,
wherein with respect to formula (II-h):

-270-



5' R^{1a}, R^{1b}, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p and r are as previously defined with respect to formula (II-a);

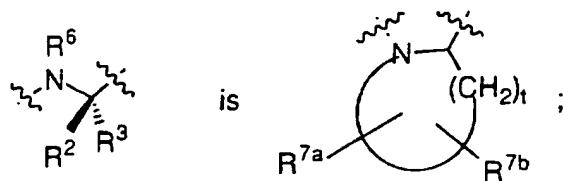
R² and R³ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group, wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

25 - R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that

-271-



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- 5 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

15

R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - 20 i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group, wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
- 25 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or
- 30

-272-

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)-;

5 R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

10

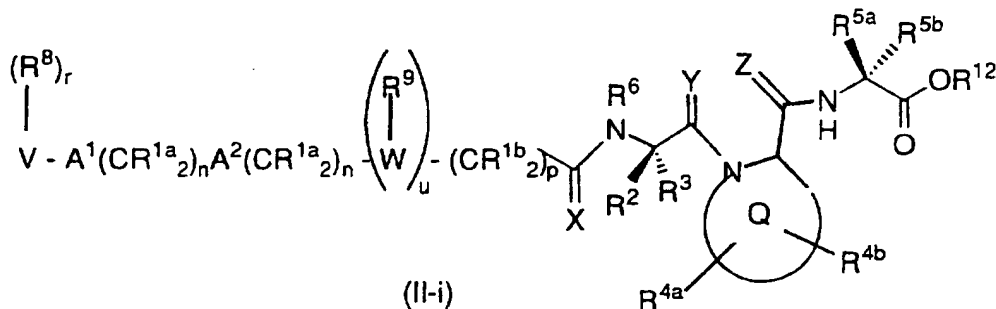
X, Y and Z are independently H₂ or O;

s is 4 or 5;

t is 3, 4 or 5; and

15 u is 0 or 1;

with respect to formula (II-i):



20

R^{1a}, R^{1b}, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p and r are as previously defined with respect to formula (II-a);

R² and R³ are independently selected from:

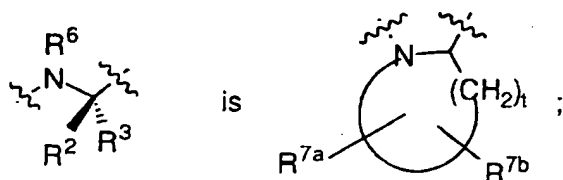
- 25 - a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or

-273-

- ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group, wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂ or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C₃-C₁₀ cycloalkyl;

-274-

R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃-, N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

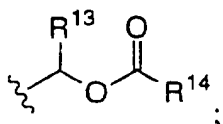
R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R¹² is

- a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:
 - 1) aryl,
 - 2) heterocycle,
 - 3) -N(R¹¹)₂,
 - 4) -OR¹⁰, or

b)



-275-

R^{13} is independently selected from hydrogen and C_1 - C_6 alkyl;

R^{14} is independently selected from C_1 - C_6 alkyl;

5

Q is a substituted or unsubstituted nitrogen-containing C_4 - C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5 - C_7 saturated ring or a heterocycle;

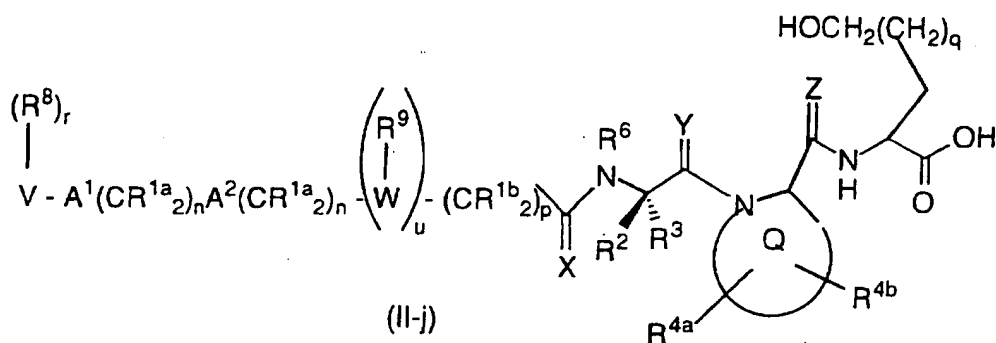
10 X , Y and Z are independently H_2 or O ;

s is 4 or 5;

t is 3, 4 or 5; and

u is 0 or 1;

15 with respect to formula (II-j):



R^{1a} , R^{1b} , R^8 , R^9 , R^{10} , R^{11} , A^1 , A^2 , V , W , m , n , p and r are as previously defined with respect to formula (II-a);

20

R^2 and R^3 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:

25

- i) methionine sulfoxide, or
- ii) methionine sulfone, and
- c) substituted or unsubstituted C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, C_3 - C_{10} cycloalkyl, aryl or heterocyclyl group,

-276-

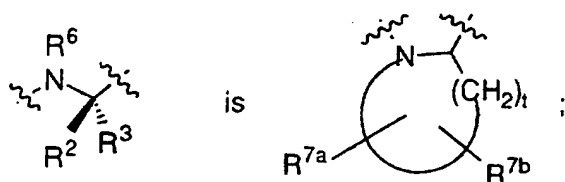
wherein the substituent is selected from F, Cl, Br,
 $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
 CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$,
 N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl,
 and

5

- d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3 - C_{10} cycloalkyl; or

10 R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^6 to form a ring such that



15

R^{4a} , R^{4b} , R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C_1 - C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N_3 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}-$, and
- d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3 - C_{10} cycloalkyl;

20

25

R^6 is independently selected from hydrogen or C_1 - C_6 alkyl;

30

-277-

Q is a substituted or unsubstituted nitrogen-containing C4-C9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C5-C7 saturated ring or a heterocycle;

5 X, Y and Z are independently H₂ or O;

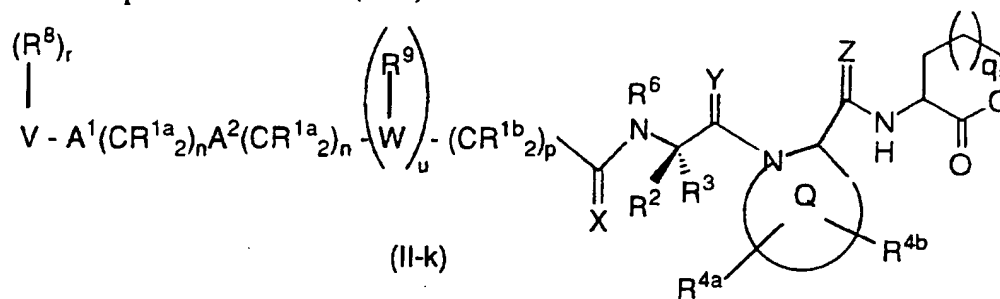
q is 0, 1 or 2;

s is 4 or 5;

t is 3, 4 or 5; and

10 u is 0 or 1;

with respect to formula (II-k):



15 R^{1a}, R^{1b}, R⁸, R⁹, R¹⁰, R¹¹, A¹, A², V, W, m, n, p, and r are as defined above with respect to formula (II-a);

R² and R³ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclyl group,

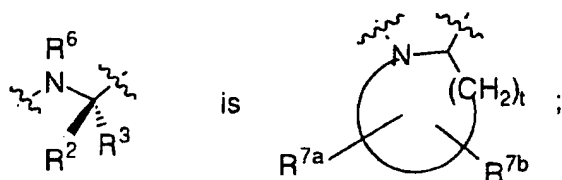
25 wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃-, N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

-278-

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁶ to form a ring such that



10

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 15 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂ or R¹¹OC(O)NR¹⁰-, and
- 20 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

25

Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

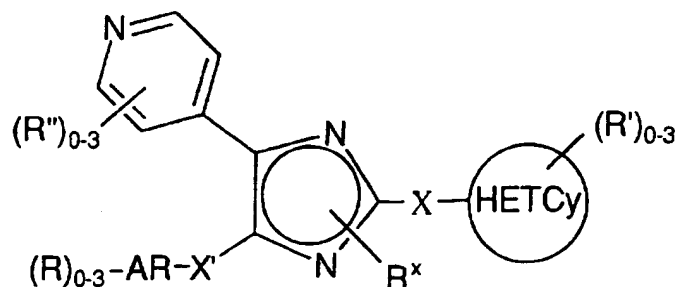
30 X, Y and Z are independently H₂ or O;

-279-

q is 0, 1 or 2;
 s is 4 or 5;
 t is 3, 4 or 5; and
 u is 0 or 1.

5

7. A method of treating cancer in accordance with claim 5 wherein the RAF antagonist is (a) a compound represented by formula (I-a):



10

(I-a)

selected from the group consisting of:

15 4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

4-[4-fluorophenyl)-3-pyridin-yl-1H-imidazol-2-yl]-1-acetyl-piperidine;

20 3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

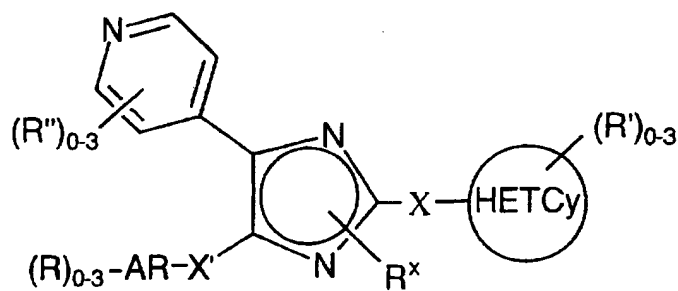
3-[4-fluorophenyl)-3-pyridin-yl-1H-imidazol-2-yl]-1-acetyl-piperidine;
 and

25 4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester,

-280-

or a pharmaceutically acceptable salt thereof.

8. A method of treating cancer in accordance with claim 5 wherein the RAF antagonist compound is (b) a compound represented by formula (I-b):



(I-b)

selected from the group consisting of:

10

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

15

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-benzyl-piperidine;

20

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-ethyl-piperidine;

4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

25

4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

-281-

- 2-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-butyl)-isoindole-1,3-dione;
- 5 2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-isoindole-1,3-dione;
- 2-(6-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-hexyl)-isoindole-1,3-dione;
- 10 4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-benzyl-piperidine;
- 2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-2,3-dihydro-isoindol-1-one ditrifluoroacetic
15 acid salt;
- 4-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-ethyl)-pyridine;
- 20 2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-1,1-dioxobenzo[d]isothiazol-3-one;
- 2-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-butyl)-1,1-dioxobenzo[d]isothiazol-3-one;
- 25 2-amino-1-{5-[4-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-ethanone dihydrochloride;
- 4-[5-(3-hydroxyphenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-
30 piperidine;
- 3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

-282-

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine:

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

5

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1,4-dimethyl-piperidine;

4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

10

4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

4-[5-(3,4-dichlorophenyl)-2-[1-(2-phenylethyl)-piperidin-4-yl]-1H-imidazol-4-yl]-pyridine;

15

4-[5-(3,4-dichlorophenyl)-2-[1-(3-phenylpropyl)-piperidin-4-yl]-1H-imidazol-4-yl]-pyridine;

20

2-(6-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-hexyl)-1,1-dioxobenzo[d]isothiazol-3-one;

2-(3-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-propyl)-1,1-dioxobenzo[d]isothiazol-3-one;

25

4-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl-methyl}-imidazol-1-yl-methyl)-benzonitrile;

4-[2-[1-(4-benzyloxybenzyl)-piperidin-4-yl-5-(3,4-dichlorophenyl)-1H-imidazol-4-yl]-pyridine; and

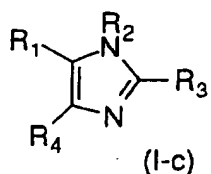
30

2-(3-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-propyl)-isoindole-1,3-dione,

-283-

or a pharmaceutically acceptable salt thereof.

9. A method of treating cancer in accordance with claim
5 5 wherein the RAF antagonist compound is (c) a compound represented
by formula (I-c):



- 10 selected from the group consisting of:

4-[4-(4-fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzamidoxime;

15 4-(1-naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

4-(1-naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;

4-(2-naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;

20 4-(2-naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(3-thiophene)-5-(4-pyridyl)imidazole;

25 4-(4-fluorophenyl)-2-(2-thiophene)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

30 4-(4-fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)imidazole;

-284-

4-(4-fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;

5

4-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-1-methyl-5-(4-pyridyl)
imidazole;

10

4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(4-methylthiophenyl)-1-(N-morpholinopropyl)-5-
(4-pyridyl)imidazole;

15

4-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-1-(N-morpholino-
propyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-1-(methylthio-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;

20

4-(4-fluorophenyl)-1-(methylsulfinyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole; and

25

4-(4-fluorophenyl)-1-(methylsulfonyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole,

or a pharmaceutically acceptable salt thereof.

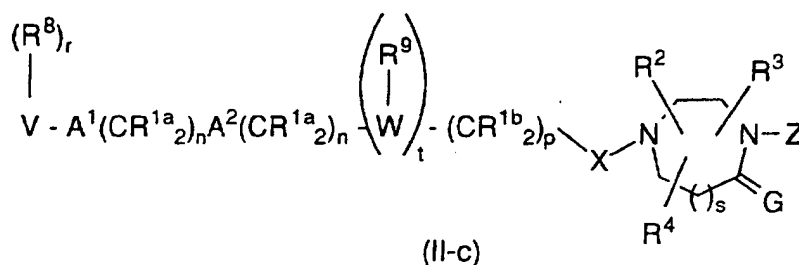
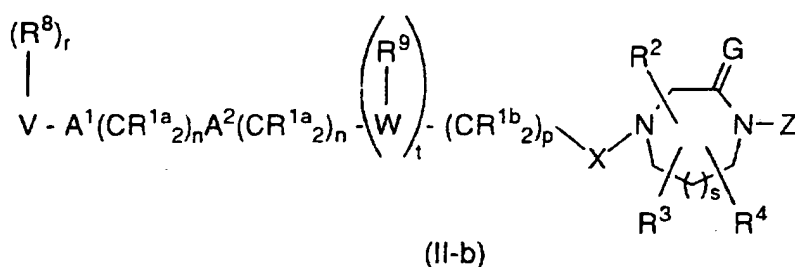
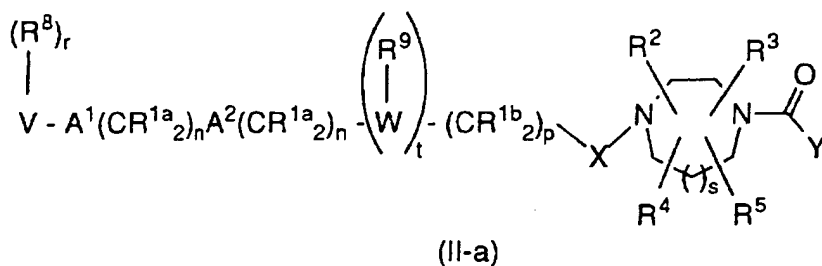
30

10. A method of treating cancer in accordance with claim 6 wherein the farnesyl transferase inhibiting compound is

(a) a compound represented by one of formulas (II-a) through (II-c):

35

-285-



selected from the group consisting of:

2(S)-butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

5

1-(3-amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol]methyl-4-(1-naphthoyl)piperazine;

10

1-[5-(1-benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;

-286-

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;

5 1-(3-acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;

10 2(R)-butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

2(S)-butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;

15 1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;

1-(2(R)-amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;

20 2(S)-benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

1-(2(R)-amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

25 1-(2(R)-amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;

30 2(S)-butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]acetyl]-4-(1-naphthoyl)piperazine;

-287-

2(S)-butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl]ethyl]-4-(1-naphthoyl)piperazine;

1-(2(R)-amino-3-hydroxypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

5

1-(2(R)-amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

10

1-(2-amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;

15

2(S)-*n*-butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;

2(S)-*n*-butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

20

1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;

2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

25

2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

30

2(S)-*n*-butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

-288-

2(S)-*n*-butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

5 2(S)-*n*-butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

10 2(S)-*n*-butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

15 1-[1-(4-bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;

20 2(S)-*n*-butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

2(S)-*n*-butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

25 1-[1-(4-phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;

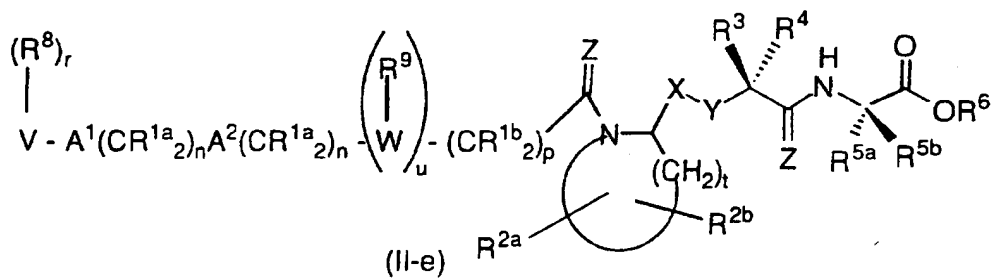
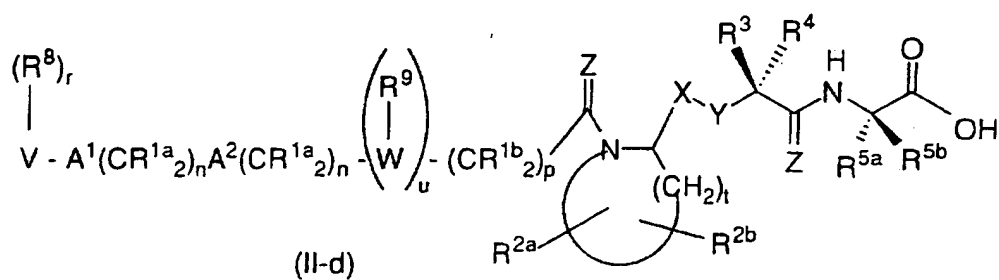
30 2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;

35 1-[[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

-289-

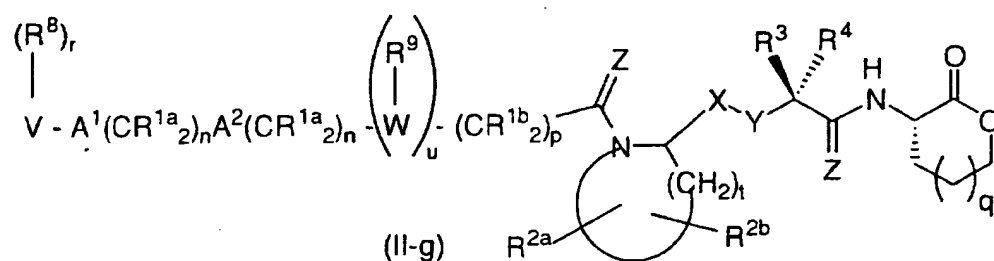
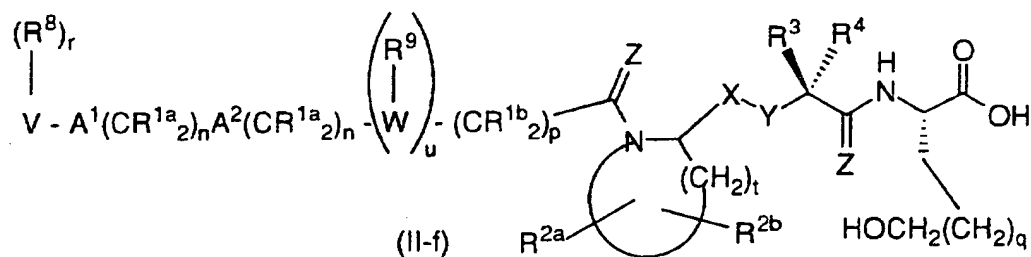
or a pharmaceutically acceptable salt thereof.

11. A method of treating cancer in accordance with claim 6 wherein the farnesyl transferase inhibiting compound is (b) a compound represented by one of formulas (II-d) through (II-g):



10

-290-



selected from the group consisting of:

- 5 N-[1-(4-imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycylmethionine
- N-[1-(4-imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;
- 10 N-[1-(2(S),3-diaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;
- N-[1-(2(S),3-diaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;
- 15 N-[1-(3-aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;
- 20 N-[1-(3-aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

-291-

N-[1-(2(S)-amino-3-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 5 N-[1-(2(S)-amino-3-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

- 10 N-[1-(3-amino-2(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-amino-2(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

15

N-[1-(L-glutaminy)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 20 N-[1-(L-glutaminy)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ;

- 25 N-[1-(L-histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(D-histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

30

N-[1-(D-histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

-292-

N-[1-(L-pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

5 N-[1-(L-pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

10 2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine isopropyl ester;

15 2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

20 2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine sulfone;

25 2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine sulfone methyl ester;

2(S)-[1-(pyrid-3-ylcarboxy)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

30 2(S)-[1-(pyrid-3-ylcarboxy)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

-293-

2(R)-{2-[1-(naphth-2-yl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenylpropionyl-methionine;

5 2(R)-{2-[1-(naphth-2-yl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(pyrid-3-ylmethyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

10 2(S)-[1-(pyrid-3-ylmethyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

15

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone isopropyl ester;

20 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

25 N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ;

30

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone methyl ester ;

-294-

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone;

5 N-[1-(sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

10 N-[1-(N,N-dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

N-[1-(N,N-dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

15 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

20 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

25 N-[1-(glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

30 N-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

-295-

N-[1-(2-acetylamino-3(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 5 N-[1-(2-acetylamino-3(S)-aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-amino-3(S)-acetylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

10

2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy]-3-phenylpropionyl-methionine methyl ester;

- 15 2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy]-3-phenylpropionyl-methionine;

2(R)-{2-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester ;

- 20 2(R)-{2-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

2(R)-{2-[1-(4-nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

25

2(R)-{2-[1-(4-nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

- 30 2(R)-{2-[1-(4-methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

2(R)-{2-[1-(4-methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

-296-

2(R)-{2-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

5 2(R)-{2-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine methyl ester;

10 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine methyl ester;

15 N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine;

20 N-[1-(seryl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(D-alanyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

25 N-[1-(1H-imidazol-4-carbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(isoasparagyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

30 N-[1-(1H-imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

35 N-[1-(3-pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

-297-

N-[1-(2-pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

- 5 N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(seryl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

10

N-[1-(D-alanyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 15 N-[1-(1H-imidazol-4-carbonyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine ;

N-[1-(isoasparagyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 20 N-[1-(1H-imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

25

N-[1-(2-pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

- 30 N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylmethyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

- 35 N-[1-(2-aminoethyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

-298-

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(2-thienyl)alanine;

- 5 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(trifluoromethyl)alanine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(2(S)-amino-4-acetylamino)butyric acid ;

10

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N,N-dimethyl)glutamine;

- 15 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine; -

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

- 20 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-methoxybenzyl)glycyl-methionine;

N-[1-(glycyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

- 25 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-((4-imidazolyl)methyl-(2S)-pyrrolidinylmethyl)-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

30

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(2-thienyl)alanine methyl ester;

- 35 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N,N-dimethyl)glutamine methyl ester ;

-299-

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(trifluoromethyl)alanine methyl ester;

- 5 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(2(S)-amino-4-acetylamino)butyric acid methyl ester;

- 10 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

- 15 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-methoxybenzyl)glycyl-methionine methyl ester;

- 20 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

N-[1-(glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(benzyl)glycyl-methionine methyl ester;

- 25 N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine cyclohexyl ester;

- 30 N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine benzyl ester;

- 35 N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ethyl ester;

-300-

N-[1-(sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

5 N-[1-(N,N-dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine (2-pyridylmethyl) ester;

10 N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine (1-glyceryl) ester;

N-[1-L-prolylpyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

15 N-[1-(L-prolyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

20 N-[1-(1-morpholinoacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1-morpholinoacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

25 N-[1-(4-piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

30 N-[1-(3-piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

-301-

N-[1-(3-piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

5 N-[1-(2-pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2-pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

10 N-[1-(4-pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

15 N-[1-(4-pyridyl(N-methyl)glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

20 N-[1-(4-pyridyl(N-methyl)glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylpropionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetyl amino)alanine;

25 N-[1-(1H-imidazol-4-ylpropionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetyl amino)alanine methyl ester;

N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetyl amino)alanine;

30 N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetyl amino)alanine methyl ester;

-302-

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -acetylamino)alanine cyclohexyl ester;

5 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(N-methyl)glutamine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(N-methyl)glutamine methyl ester ;

10 N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -methylcarbonylamino)alanine;

15 N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -methylcarbonylamino)alanine methyl ester ;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -methylsulfonylamino)alanine;

20 N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -methylsulfonylamino)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -propionylamino)alanine ;

25 N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -propionylamino)alanine methyl ester;

30 N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -pyrrolidinon-1-ylamino)alanine;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β -pyrrolidinon-1-ylamino)alanine methyl ester ;

-303-

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine;

5 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

10 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine;

15 N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine methyl ester;

20 N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

25 N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

30 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-cyanobenzyl)glycyl-methionine;

-304-

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-cyanobenzyl)glycyl-methionine methyl ester ;

5 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-cyanobenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

10 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

15 N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

20 N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

25 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methylbenzyl)glycyl-methionine;

30 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methylbenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-trifluoromethylbenzyl)glycyl-methionine;

-305-

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(2-trifluoromethylbenzyl)glycyl-methionine methyl ester;

5 N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylsulfonyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylsulfonyl)glycyl-methionine methyl ester;

10 N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 4-N-methylpiperidinyl ester;

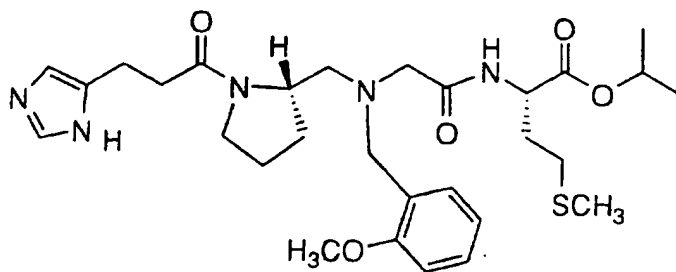
N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine tert-butyl ester;

15 N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 3-pentyl ester;

20 N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

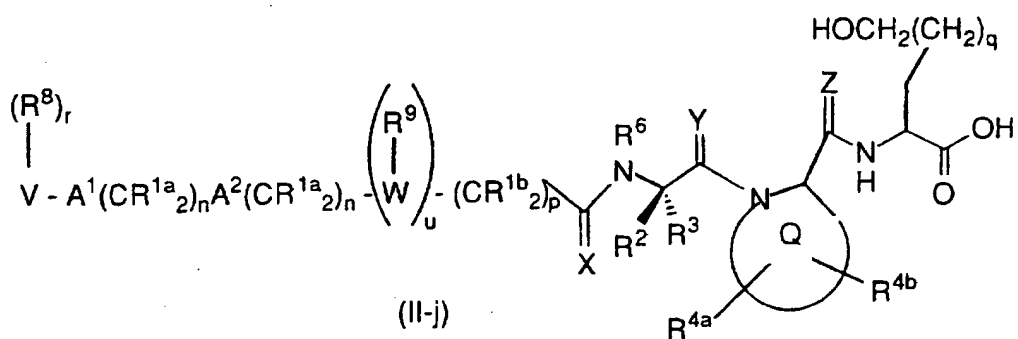
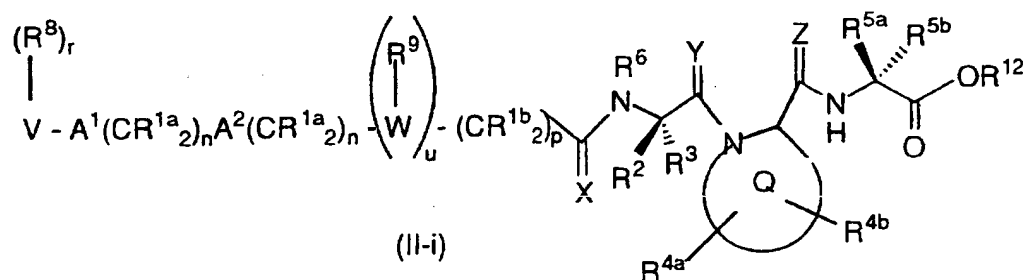
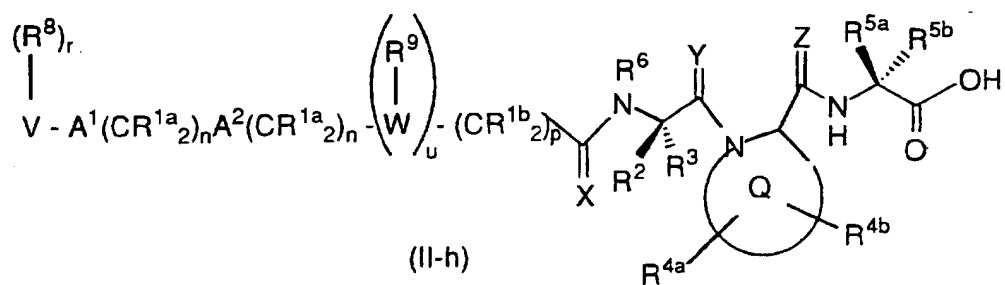
25 N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester



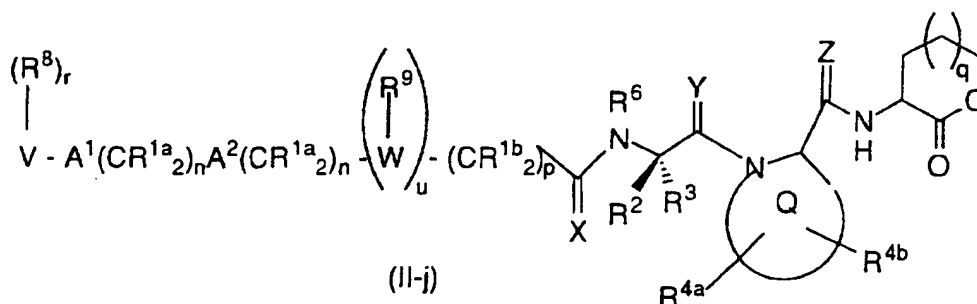
or a pharmaceutically acceptable salt thereof.

-306-

11. A method of treating cancer in accordance with claim
6 wherein the farnesyl transferase inhibiting compound is
5 (c) a compound represented by one of formulas (II-h) through (II-k):



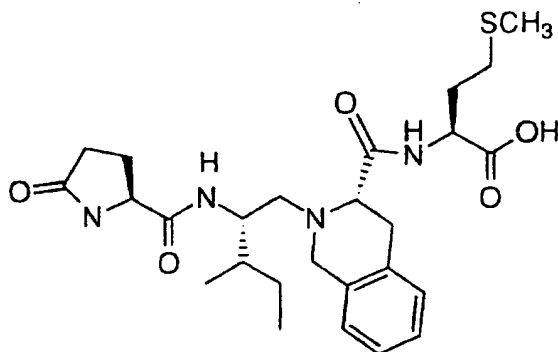
-307-



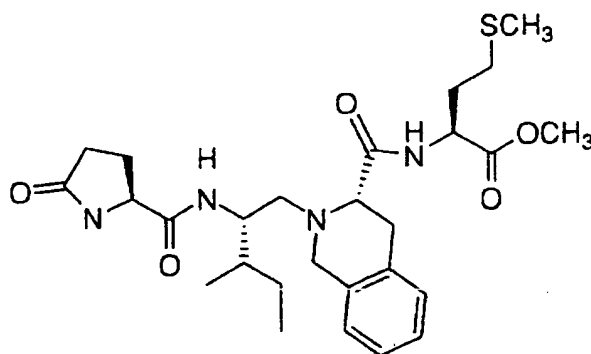
selected from the group consisting of:

- 5 N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester;
- 10 N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine;
- 15 N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester;
- N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine;
- 20 N-[1-glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine methyl ester;
- N-[1-glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine;
- 25 N-[L-pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine

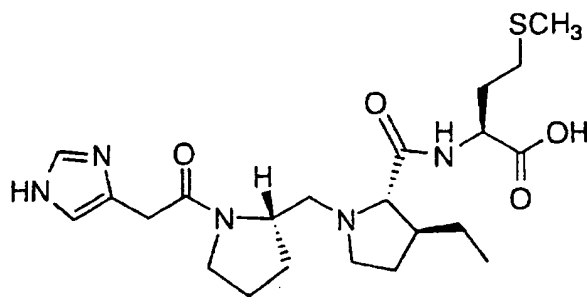
-308-



N-[L-pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester

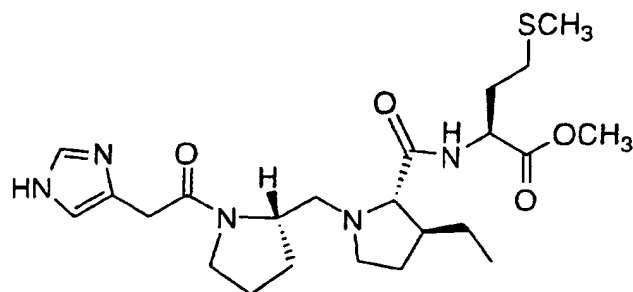


- 5 N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylpropyl-methionine

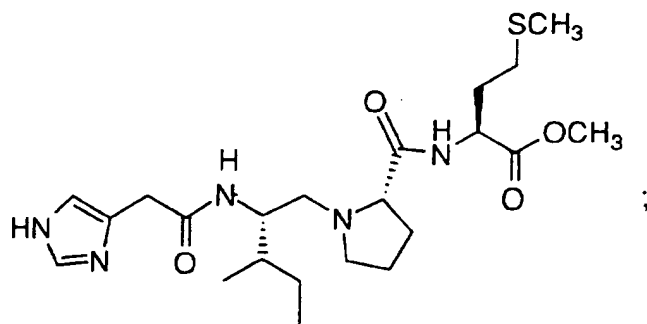


- N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylpropyl-methionine methyl ester

-309-

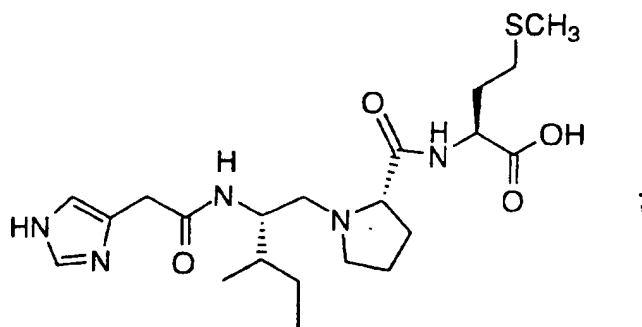


N-[(1H-imidazol-4-ylacetyl)-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester



5 and

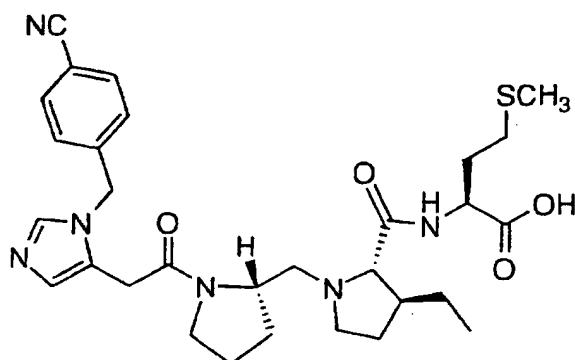
N-[(1H-imidazol-4-ylacetyl)-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine



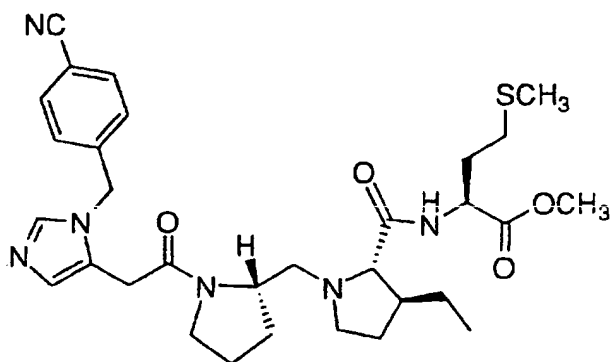
10

(N-[1-cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl)-3(S)-ethyl-prolyl methionine;

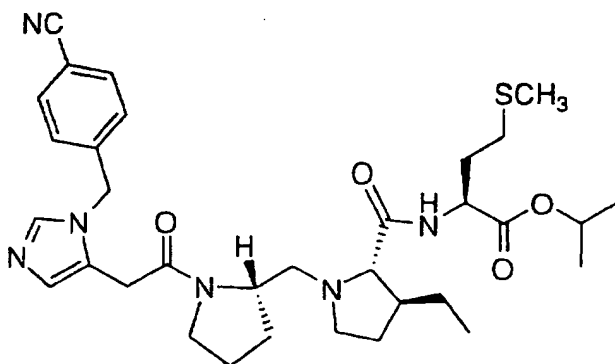
-310-



(N-[1-cyanobenzyl]-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-
 5 3(S)-ethyl-prolyl methionine methyl ester;



(N-[1-cyanobenzyl]-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-
 10 3(S)-ethyl-prolyl methionine isopropyl ester, and



-311-

or a pharmaceutically acceptable salt thereof.

12. A method in accordance with claim 1 wherein the farnesyl protein
5 transferase inhibiting compound is selected from the group consisting
of:

(S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-imidazolylmethyl]-5-[2-
(methanesulfonyl)ethyl]-2-piperazinone dihydrochloride;

10

1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolyl-methyl]-2-
piperazinone dihydrochloride;

- 15 N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-
methoxybenzyl)glycyl-methionine isopropyl ester;

(N-[1-Cyanobenzyl)-1H-imidazol-5-yl]acetyl]pyrrolidin-2(S)-ylmethyl]-
3(S)-ethyl-prolyl methionine isopropyl ester;

- 20 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-
dimethylphenyl)piperazin-5-one;

- N-[2(S)-N'-(1-(4-Cyanophenyl-methyl)-1H-imidazol-5-ylacetyl)amino-
3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester
25 and

- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester,
30 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05328

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/44, 31/495

US CL : 514/255, 341

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/255, 341

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,352,705 A (DEANA ET AL.) 04 October 1994, whole document.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A documents defining the general state of the art which is not considered to be of particular relevance	X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 JUNE 1997	Date of mailing of the international search report 11 JUL 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD L. RAYMOND Telephone No. (703) 308-1235